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[1] J. B. Austin and R. H. H. Pierce, *J. Amer. Chem. Soc.* 55, 661 (1933).

[2] J. R. Goldsmith, D. L. Graft and O. I. Joensuu, *Geochim. et Cosmochim. Acta* 7, 221 (1955).

[3] S. T. Yoffe and A. N. Nesmeyanov, *Handbook of Magnesium-Organic Compounds* Vol. II, p. 239. Pergamon Press, London (1956).

Abbreviations are used freely in *Tetrahedron*, particularly in setting the experimental section. For the most part these are not followed by a full stop (period). Among the more commonly used abbreviations, these may be listed:

g kg mm cm ml cc cm^3 sec min hr n_D^{25} $[\alpha]_D^{25}$ 25° (without C which is always understood) but m.p., b.p., l. (litre), in. (inch) but in^3.

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THE REACTION OF DICHLOROCARBENE WITH AMINES*

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Sterling Chemistry Laboratory, Yale University, New Haven, Connecticut

(*Received* 7 *April* 1960)

Abstract—Dichlorocarbene reacts with secondary amines to give the derived formamide. With tertiary amines, amides are obtained which are the result of rearrangements and Hofmann eliminations in an intermediate nitrogen ylid. In one case, trimethylamine, a compound was obtained whose analysis and properties are consistent with those expected for α,α,β-trichloroethyldimethylamine, V.

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THE intermediacy of dichlorocarbene in the basic hydrolysis of chloroform first suggested in 1862 by Geuther[1] has now been convincingly demonstrated by the kinetic results obtained by Hine[2] and by the structural evidence presented by Doering and Hoffmann[3]. The carbylamine test for primary amines, discovered in 1870 by Hofmann[4], has been interpreted as the reaction of dichlorocarbene with the amine by Nef[5] and later by Hine[2]. Recently Smith and Kalenda[6], in the preparation of various substituted isonitriles, reported the isolation of a small amount of 3-diethylaminopropylformamide when 3-diethylaminopropylamine was treated with chloroform and potassium hydroxide. These authors attribute the formation of the amide product to the hydrolysis of the dichloromethylamine intermediate resulting from the addition of dichlorocarbene to the primary amine. Thus, the dichloromethylamine intermediate in the case of primary amines generally proceeds to the isonitrile but may give the formamide derivative in some cases.

The object of this study was to determine the nature of the products, if any, resulting from the reaction of dichlorocarbene with secondary and tertiary amines. A series of secondary amines was treated under conditions where it has been clearly established[3] that dichlorocarbene is produced. A benzene solution of chloroform was added, dropwise, to stirred mixtures of the amine, benzene, and potassium t-butylate. Precautions were taken to exclude water prior to, and during the reaction. The reactions proceeded smoothly to give varying yields of the derived formamide. Diethylamine, dimethylamine, diphenylamine, and piperidine were treated in the manner described to give diethylformamide, dimethylformamide, diphenylformamide, and N-formylpiperidine, respectively. Yields varied from 31 per cent in the piperidine case to 0·3 per cent in the case of diphenylamine. The poor yield from diphenylamine can be attributed to its very weak basicity. The reactions were invariably accompanied by the production of large quantities of brown polymeric material. When the reactions were carried out without using benzene as solvent for the chloroform and

* Preliminary Communication: *Tetrahedron* **6**, 88 (1959).

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[1] A. Geuther, *Liebigs Ann.* **123**, 121 (1862).

[2] J. Hine, *J. Amer. Chem. Soc.* **72**, 2438 (1950).

[3] W. E. Doering and A. K. Hoffmann, *J. Amer. Chem. Soc.* **76**, 6162 (1954).

[4] A. W. Hofmann, *Ber. Dtsch. Chem. Ges.* **3**, 767 (1870).

[5] J. U. Nef, *Liebigs Ann.* **298**, 367 (1897).

[6] P. A. S. Smith and N. W. Kalenda, *J. Org. Chem.* **23**, 1599 (1958).

potassium t-butylate, the yield of amide was reduced and the amount of polymeric material produced was increased. Likewise, carrying out the reaction at room temperature led to reduced yields.

The reaction probably proceeds by an attack of dichlorocarbene on the amine to give the expected dichloromethylamine intermediate, I, such as has been postulated by Smith and Kalenda[6]. This intermediate then proceeds to the observed amide under the reaction conditions or work-up.

$$R_2NH + :CCl_2 \rightarrow R_2\overset{+}{N}(H)-CCl_2^- \rightarrow R_2N-CCl_2H$$

$$R_2N-CCl_2H \rightarrow R_2N-CHO \qquad \text{I}$$

Since preliminary publication of these results Frankel *et al.*[7] have published similar results and have expressed agreement with the mechanism presented above.

Attempts to isolate the dichloromethylamine intermediate were unsuccessful. Dichloromethylamines are not known in the pure state although they have been suggested as intermediates by several authors. Thus, Hinkel and Watkins[8] have claimed the formation of dichloromethylamine itself (formamidodichloride) by treating hydrogen cyanide with hydrogen chloride. The presence of the amine is suggested by its condensation with nitrobenzaldehydes to give, eventually, nitrobenzylidenebisformamides. The initial condensation product between the nitrobenzaldehyde and dichloromethylamine could not be isolated. These same authors claim the formation of acetamidodichloride, from the action of hydrogen chloride on acetonitrile, as unpublished work, Recently, however, Janz and Danyluk[9] made a similar study but these authors favor a nitrilium salt structure, $[CH_3CNH^+\ ClHCl^-]$, for the crystalline compound formed. They indicate that no evidence was found for the acetamidodichloride structure.

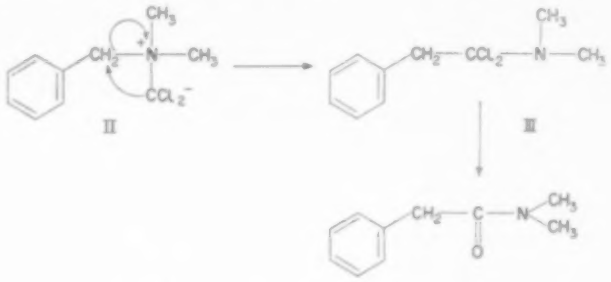
Wallach[10–12] and von Braun[13,14] have postulated the formation of amidodichlorides when amides are treated with phosphorus pentachloride. The amidodichlorides were not isolated, however. Stephen and Bleloch[15] have isolated the hydrochloride of N-phenylbenzamidodichloride as large yellow prisms. Hallman[16] reported the formation of dimethylbenzamidodichloride when dimethylbenzamide was treated with phosgene. The author described this product as unstable and deliquescent.

In view of the reported instability of the dichloromethylamines it seems reasonable to assume that this intermediate was hydrolyzing to the observed amide, despite precautions taken to exclude water during the reaction.

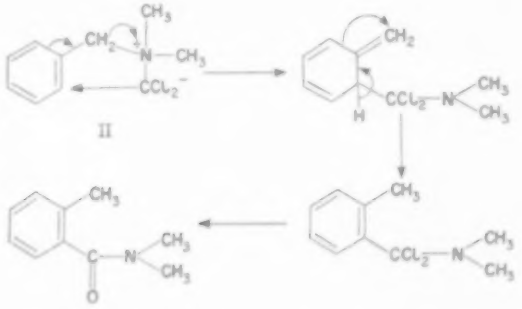
When diethylamine, aqueous sodium hydroxide and sodium formate were placed together under the conditions of the reaction, no amide was formed. Thus the trivial explanation involving prior basic hydrolysis of the chloroform to formate, followed by reaction with amine to give amide, is precluded.

[7] M. B. Frankel, H. Feuer and J. Bank, *Tetrahedron Letters* No. 7, 5 (1959).
[8] L. E. Hinkel and T. I. Watkins, *J. Chem. Soc.* 647 (1944).
[9] G. J. Janz and S. D. Danyluk, *J. Amer. Chem. Soc.* **81**, 3850 (1959).
[10] O. Wallach, *Liebigs Ann.* **237**, 251 (1887).
[11] O. Wallach, *Liebigs Ann.* **214**, 193 (1882).
[12] O. Wallach, *Liebigs Ann.* **184**, 1 (1877).
[13] J. von Braun, *Ber. Dtsch. Chem. Ges.* **37**, 2678 (1904).
[14] J. von Braun and J. Weismantel, *Ber. Dtsch. Chem. Ges.* **55**, 3165 (1922).
[15] H. Stephen and W. Bleloch, *J. Chem. Soc.* 886 (1931).
[16] F. Hallmann, *Ber. Dtsch. Chem. Ges.* **9**, 846 (1876).

When tertiary amines were subjected to the conditions described above a variety of products was observed depending upon the structure of the amine used. Benzyldimethylamine reacted to give N,N-dimethylphenylacetamide and dibenzyl. Formation of the amide product is most likely due to a Stevens rearrangement of the initially-formed nitrogen ylid. This rearrangement, first reported by Stevens *et al.*[17], involves a 1,2 shift of a methyl, benzyl, substituted benzyl, phenacyl, allyl, or 3-phenylpropargyl group in quarternary ammonium ions. Migration of a benzyl group in the initial ylid, II, formed by addition of dichlorocarbene to benzyldimethylamine, followed by hydrolysis of the amidodichloride, III, could explain the observed product.



The ylid, II, presumably also could undergo a rearrangement of the type reported by Sommelet[18]. Such a rearrangement involves attack in the aromatic nucleus *ortho* to the substituent followed by rearomatization of the intermediate exomethylene compound. The hydrolyzed product of such a rearrangement in this case would be N,N-dimethyl-O-toluamide. None of this product could be detected in the reaction mixture.



Whether a particular quarternary ammonium ion will undergo the Stevens or Sommelet rearrangement, or both, seems to depend on the base and conditions used. Benzyltrimethylammonium, benzhydryltrimethylammonium and dibenzyldimethylammonium ions are all known to give Stevens or Sommelet rearrangements depending on the conditions.[19–22] Phenyl lithium, hydroxide or methoxide tended to give

[17] T. S. Stevens, E. M. Creighton, A. B. Gordon and M. McNicol, *J. Chem. Soc.* 3193 (1928).
[18] M. Sommelet, *C.R. Acad. Sci., Paris.* **205,** 56 (1937).
[19] G. Wittig, R. Mangold and G. Felletschin, *Liebigs Ann.* **560,** 116 (1948).
[20] C. K. Ingold and E. D. Hughes, *J. Chem. Soc.* 69 (1933).
[21] T. Thomson and T. S. Stevens, *J. Chem. Soc.* 1932 (1932).
[22] S. W. Kantor and C. R. Hauser, *J. Amer. Chem. Soc.* **73,** 4122 (1951).

Stevens rearrangements, while sodamide in liquid ammonia favored Sommelet rearrangements.

The formation of products analgous to the dibenzyl product isolated has been observed by other workers. Thus, Stevens *et al.*[23] found that when phenacyl-*p*-nitrobenzyldimethylammonium bromide was treated with base the rearrangement product, *o*-dimethylamino-*o*-*p*-nitrobenzylacetophenone, was obtained, along with *p*-nitrotoluene and *p,p'*,-dinitrodibenzyl. Likewise, Wittig *et al.* [19] upon treating benzhydryltrimethylammonium bromide with phenyl lithium obtained tetraphenylethane in addition to the Stevens and Sommelet rearrangement products.

Previous work on the mechanism of the Stevens rearrangement[17,24–28] indicates that an ylid is formed which rearranges with migration of a group from nitrogen to carbon. In some cases apparently, elimination of this group as an anion can occur. Protonation of the anion can then give the corresponding hydrocarbon. Alternatively alkylation of this anion by another quarternary ammonium ion[22,29] can give the observed coupling products. The ammonium cation left by this elimination would be expected to give a carbonyl containing product on work up. Such a product has been isolated.[22]

The formation of dibenzyl in the reaction between benzyldimethylamine and dichlorocarbene can be explained using these steps. The initially formed ylid, II, can eliminate a benzyl anion which can then be benzylated by the quarternary salt formed when the ylid is protonated. t-Butyl alcohol may act as a source of protons to give this quarternary salt.

When triethylamine was treated with chloroform and potassium t-butylate two amide products were obtained. The products were separated by gas chromatography and were identified as diethylformamide, (15·2%) and N,N,-diethyl-α-chloropropionamide, (12·2%). The formation of diethylformamide is most likely due to a β-elimination in the initially-formed ylid, IV, followed by hydrolysis of the diethyldichloromethylamine.

$$(CH_3{-}CH_2)_3N + :CCl_2 \rightarrow (CH_3{-}CH_2)_3\overset{+}{N}{-}CCl_2^- \qquad \text{IV}$$

$$(CH_3{-}CH_2)_2\overset{+}{N}(CCl_2^-)(H)(CH_2{-}CH_3) \rightarrow CH_2{=}CH_2 + (CH_3{-}CH_2)_2\overset{+}{N}{-}CCl_2H$$

$$(CH_3{-}CH_2)_2N{-}CCl_2H \rightarrow (CH_3{-}CH_2)_2N{-}CHO$$

Weygand *et al.*[30], in an investigation of the Hofman degradation of quarternary ammonium salts using isotopic hydrogen have found that an α hydrogen can be abstracted initially which, in turn, can abstract the β hydrogen leading to olefin formation. The ylid, IV, is, therefore, expected to decompose, at least partially, to give the observed diethylformamide.

[23] T. S. Stevens, W. W. Spedden, E. T. Stiller and T. Thomson, *J. Chem. Soc.* 2119 (1930).
[24] T. S. Stevens and B. A. Hems, *J. Chem. Soc.* 856 (1937).
[25] T. S. Stevens and T. Thomson, *J. Chem. Soc.* 69 (1932).
[26] T. S. Stevens and T. Thomson, *J. Chem. Soc.* 55 (1932).
[27] T. S. Stevens and J. L. Dunn, *J. Chem. Soc.* 1926 (1932).
[28] T. S. Stevens, *J. Chem. Soc.* 2107 (1932).
[29] H. R. Snyder, C. W. Smith and J. M. Stewart, *J. Amer. Chem. Soc.* **66**, 200 (1944).
[30] F. Weygand, H. Daniel and H. Simon, *Chem. Ber.* **91**, 1691 (1958).

The other product shows the infrared spectrum of an amide. The nuclear magnetic resonance spectrum (NMR) of this compound is shown in Fig. 1.

When the sample is heated and its NMR spectrum retaken then two groups peaks of at 6·77 and 8·90* collapse to a quadruplet and a triplet, respectively (Spectrum 2b in Fig. 1). These peaks are assigned to the methylene and methyl groups of a diethyl-substituted amide.

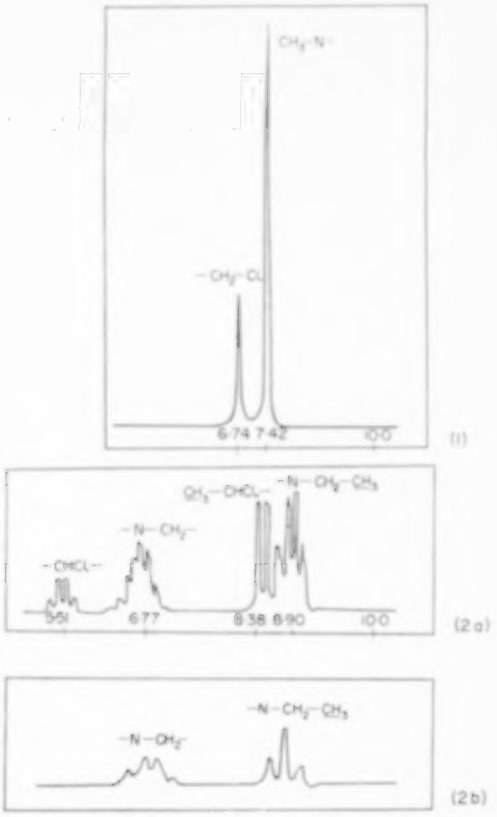


FIG. 1. Nuclear magnetic resonance spectra. (1) V in CS_2, (2a) α-Chlorodiethylpropionamide in CCl_4 at room temperature, (2b) 8·90 and 6·77 peaks of XIII at ca. 80°. Chemical shift values are in p.p.m. relative to tetramethylsilane (= 10·0 p.p.m.).

There is restricted rotation about the C–N bond because of amide resonance and at room temperature the two ethyl groups attached to the nitrogen atom are non-equivalent.[31,32] When the amide is heated the barrier to rotation is passed rapidly, the diethylamino group rotates freely and the two ethyl groups become equivalent leading to a single ethyl group spectrum. The spectrum also has a doublet at 8·38 and a quadruplet at 5·51 which are assigned to the remaining methyl group and the α hydrogen of N,N-diethyl-α-chloropropionamide, respectively.

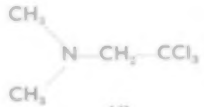
* NMR values given are chemical shifts in p.p.m. with tetramethylsilane = 10·00 p.p.m.

[31] W. D. Phillips, *J. Chem. Phys.* **23**, 1363 (1955).

[32] H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.* **25**, 1228 (1956).

Trimethylamine was liquified at −20° and then treated as described previously. In this case, the evaporative distillation used to separate the crude reaction product from tars produced in the reaction was characterized by the production of an acidic gas and the sublimation of a tan-colored solid. The solid sublimate was resublimed several times and could be obtained as a pale yellow solid. This solid turned brown upon standing. It decomposed at ca. 185°. The reaction also gave a liquid product, V, $C_4H_8NCl_3$, which could be distilled at reduced pressure and had b.p. 50·5° (11 mm). When distillation was attempted at atmospheric pressure the liquid decomposed rapidly giving off an acidic gas. The NMR spectrum of the pure compound (Fig. 1) was very simple, consisting of two sharp peaks in an approximate three to one ratio. These peaks had τ values of 7·42 and 6·74 for the stronger and weaker peaks, respectively. When the solid product of the reaction was treated with aqueous base it gave a liquid whose infrared spectrum was identical with that of the liquid product. When a benzene solution of V was treated with aqueous silver nitrate an immediate, copious, white precipitate was formed. The product of this reaction had a gas phase chromatography retention time which was identical with that for authentic N,N-dimethyl-α-chloroacetamide. The infrared spectrum of a sample of this component was superimposable on that of authentic N,N-diethyl-α-chloroacetamide. On the basis of the evidence given the liquid product, V, appears to be a chloro-amine. The solid product obtained is undoubtedly the hydrochloride of this amine, the HCl being produced by partial decomposition of V during distillation. The infrared spectrum of V indicates that it is a tertiary amine since there is no NH absorption. Since the NMR spectrum indicates that the compound has only two kinds of protons and these in a three to one ratio, only structures V and VI would seem to warrant consideration for the chloroamine. Compound VI would not be expected to react with silver nitrate.

V



VI

Compound V, on the other hand, should react with aqueous silver nitrate to give N,N-dimethyl-α-chloroacetamide the observed product. On the basis of the evidence given the amine isolated is believed to be, V, α,α,β-trichloroethyldimethylamine.

The mechanism for the formation of V from trimethylamine is undoubtedly the same as that for the formation of N,N-diethyl-α-chloropropionamide in the triethylamine reaction. However, V, does not appear to hydrolyze to the amide as readily. An attempt to prepare an authentic sample of this amine from the amide and phosphorus pentachloride failed.

No final conclusion about the mechanisms of the last two reactions described can be drawn at this time. However, certain aspects of the reaction deserve comment. Apparently an α,α,β trichloro amine is formed in each case, but hydrolyzed during work-up in the triethylamine reaction. It may be noted that this is the expected result of a Stevens rearrangement where the product has been chlorinated. The ultimate source of this extra chlorine must be chloroform. In strong base, the most

likely mechanism for chlorination is "positive halogen transfer",[33–41] which is nucleophilic displacement on halogen. The halogen donor may be chloroform itself or some reaction product. t-Butyl hypochlorite may well be the actual chlorinating agent as suggested[42] in explanation of a reaction performed under similar conditions.

Since no normal product of the Stevens rearrangement is obtained, and since the chlorination is specific, it may be that the chlorination occurs at a stage before the rearrangement: however, elimination of HCl from the normal Stevens product followed by chlorination of the resulting eneamine has not been ruled out. Further work, which may illuminate the mechanism, is in progress.

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EXPERIMENTAL*

Reaction of chloroform, potassium t-butylate, and diethylamine. The reaction of potassium metal (23·5 g, 0·6 mole) and 0·6 l. dried (distilled from calcium hydride) t-butyl alcohol was carried out with stirring at room temp in a 1 l. three-necked flask equipped with a reflux condenser and drying tube and kept under a slight positive pressure of prepurified nitrogen. After the potassium had completely dissolved, excess t-butyl alcohol was removed by distillation. The dry powder remaining was further dried at 160–170° at 1–2 mm for 6 hr. To a slurry of the dried powder with 350 ml dry benzene was added 100 ml (71·0 g, 0·97 mole) diethylamine which had been carefully fractionated. The flask contents were stirred in a dry ice-trichloromethylene bath maintained at ca. 5–10°. A solution of 33·1 ml (47·9 g, 0·4 mole) chloroform in 100 ml dry benzene was added, dropwise, to the stirred reaction mixture. When all the chloroform solution had been added the dark brown mixture was allowed to warm to room temp and stirred for an additional 0·5 hr. The reaction mixture was concentrated *in vacuo*. Ether was added to the dark residue to precipitate potassium chloride which was filtered off and washed with ether. The filtrate was transferred to a distillation apparatus. After removal of ether, benzene, and t-butyl alcohol a fraction was obtained at 64° and 10 mm. The infrared spectrum of this material was superimposable with that of authentic diethylformamide; lit.[43] b.p. 177–179° (760 mm). Yield was 9·0 g (22·5% based on chloroform).

When this preparation was carried out at room temp or without using benzene as solvent the yield was reduced to ca. 10–15%.

When the amine is treated with sodium formate no amide is produced. To a solution of 17·7 g (0·24 mole) diethylamine in 100 ml benzene was added 10 g (0·15 mole) sodium formate and the mixture stirred at room temp for 4 hr. After adding 100 ml NaOH, (10% aqueous solution) stirring was continued for an additional hour. The benzene layer was separated off and concentrated to ca. 10 ml. An infrared spectrum of the residue showed no amide present.

Reaction of dimethylamine, chloroform, and potassium t-butylate. A slurry was made of benzene and potassium t-butylate, produced by dissolving 38·3 g (0·98 mole) potassium metal in 600 ml t-butyl alcohol and removing excess alcohol. Chloroform (117·5 g, 0·98 mole) in benzene solution was added dropwise to a stirred mixture of the slurry and 11·0 g (0·24 mole) dimethylamine in a 1 l., three-necked flask equipped with a dry ice condenser. The flask was cooled to ca. −10° in a dry ice-trichloroethylene bath. When chloroform addition was complete the reaction mixture was allowed to warm to room temp and was stirred for an additional 0·5 hr. The reaction mixture was extracted

* All melting and boiling points are uncorrected. Infrared spectra were taken with a Perkin–Elmer Corporation model 21 recording infrared spectrophotometer. Nuclear magnetic resonance spectra were taken with a Varian Associates 60 mc. high resolution nuclear magnetic resonance spectrometer. Gas chromatograms were run on a Wilkins Instrument and Research Aerograph model A-90-C gas chromatograph. Analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside 17, N.Y.

[33] M. Ballester, C. Molinet and J. Rosa, *Tetrahedron* **6**, 109 (1959).
[34] R. Altschul and P. D. Bartlett, *J. Org. Chem.* **5**, 623 (1940).
[35] J. E. Leffler, *J. Amer. Chem. Soc.* **75**, 3598 (1953).
[36] M. F. Hawthorne, *J. Amer. Chem. Soc.* **77**, 5739 (1955).
[37] H. Finkelstein, *Ber. Dtsch. Chem. Ges.* **43**, 1528 (1910).
[38] J. V. Backus, R. W. West and M. A. Whitely, *J. Chem. Soc.* 359 (1921).
[39] R. Willstätter and V. Hottenroth, *Ber. Dtsch. Chem. Ges.* **37**, 1775 (1904).
[40] M. Weizmann and J. Edlitz, *Bull. Soc. Chim. Fr.* **53**, 1495 (1933).
[41] A. Perret and R. Perrot, *Bull. Soc. Chim. Fr.* **1**, 1547 (1934).
[42] W. E. Parham, F. C. Loew and E. E. Schweizer, *J. Org. Chem.* **24**, 1900 (1959).
[43] O. Wallach, *Liebigs Ann.* **214**, 271 (1882).

with 300 ml water and the aqueous layers backwashed with ether. The combined ether and benzene solutions were dried over magnesium sulfate. The ether and benzene were distilled out *in vacuo*. The dark residue was distilled in an evaporative still. The fraction boiling from 80–165° at 20 mm was redistilled through a fractional column. Dimethylformamide (2·03 g, 11·3%) distilled out at 59° (19 mm). The infrared spectrum of the product was superimposable with that of an authentic sample of dimethylformamide.

Reaction of piperidine, chloroform, and potassium t-butylate. To a slurry of potassium t-butylate, prepared from 34·2 g (0·87 mole) potassium metal and 200 ml benzene was added 86·2 g (1·01 mole) of redistilled piperidine. The reaction flask was cooled to ca. 5° in a dry ice-trichloroethylene bath. A solution of 47·9 g (0·4 mole) chloroform in 100 ml benzene was added, dropwise, to the stirred reaction mixture. When addition was complete, the reaction mixture was allowed to warm to room temp and was stirred for an additional 0·5 hr. The benzene solution was concentrated *in vacuo* and ether added to precipitate potassium chloride. The potassium chloride was filtered off and washed well with ether. The combined benzene and ether solutions were distilled *in vacuo*. After removal of ether, benzene and t-butyl alcohol the amide distilled at 80° (3 mm), lit.[44] b.p. 108° (14–15 mm). Yield was 14·0 g (31%). The infrared spectrum of the product was identical to that of an authentic sample of N-formyl piperidine prepared by refluxing piperidine with formic acid.

Reaction of diphenylamine, chloroform, and potassium t-butylate. A solution of 28·9 g (0·24 mole) chloroform in 80 ml benzene was added, dropwise, at room temp, to a slurry of 200 ml benzene and 5·74 g (0·051 mole) potassium t-butylate to which had been added 6·9 g (0·041 mole) redistilled diphenylamine. When addition of the chloroform solution was complete, 100 ml water was added and stirring was continued at room temp for an additional hour. The benzene layer was separated and concentrated by distillation *in vacuo*.

A portion (ca. 21 ml) of the dark, crude residue was placed on a column of alumina (ca. 100 g). Elution with benzene : ether; 9:1 gave a solid whose infrared spectrum was identical to that of an authentic sample of diphenylformamide. Yield, by quantitative infrared measurement, was 0·028 g (0·34%).

The authentic sample was prepared by refluxing 24·9 g (0·14 mole) diphenylamine with 183 g (4·0 mole) formic acid for 144 hr. The reaction mixture was then poured into water. The white crystals obtained were filtered off and recrystallized from ethanol–water, m.p. 68·5°.

Reaction of triethylamine, chloroform, and potassium t-butylate. To a slurry of alcohol-free potassium t-butylate, prepared by dissolving 34·4 g (0·88 mole) potassium metal in t-butyl alcohol, and 400 ml benzene, was added 31 ml (22·4 g, 0·22 mole) triethylamine. The amine had been carefully fractionated through a column packed with metal helices. To the stirred flask contents, cooled to 5°, was added, dropwise, a solution of 70·8 ml (106 g, 0·88 mole) chloroform in 400 ml benzene. The flask contents were stirred at room temp for an additional 0·5 hr following addition of the chloroform solution. The dark reaction mixture was then washed with water and the aqueous layers backwashed with ether. The combined ether–benzene solution was dried with magnesium sulfate. The dried solution was concentrated by distillation *in vacuo*. The dark, viscous residue was transferred to an evaporative still. After removal of most of the benzene and t-butyl alcohol, all the remaining volatile material was collected as a second fraction. Analysis of this fraction by gas phase chromatography showed the presence of two major products. One of the products had the same retention time as authentic diethylformamide. Its infrared spectrum was superimposable with that of authentic diethylformamide. Yield was 3·4 g (15·2%). The second component had a longer retention time than diethylformamide. Its infrared spectrum indicated the presence of a disubstituted amide. The NMR spectrum of this compound had a quartet at 5·51, a complex peak at 6·77, methyl peaks at 8·38, and a complex peak at 8·90. When heated, the peaks at 6·77 and 8·90 became a quartet and triplet, respectively. The behavior of the peaks at 6·77 and 8·90 is strong evidence for the presence of a diethyl-substituted amide. The quartet at 5·51 and the methyl peaks at 8·38 are assigned to the methine and remaining methyl protons of N,N-diethyl-α-chloro-propionamide, respectively. Yield was 4·38 g (12·15%). (Found: C, 51·6; H, 8·74; Cl, 21·6; N, 8·58. Calc. for $C_7H_{14}ClNO$: C, 51·4; H, 8·62; Cl, 21·7; N, 8·56%).

Reaction of benzyldimethylamine, chloroform, and potassium t-butylate. To a slurry of alcohol-free potassium t-butylate (from 32·8 g, 0·84 mole potassium metal) and 500 ml benzene was added 28·6 g (0·21 mole) benzyldimethylamine. The amine was prepared from the reaction of benzyl

[44] O. Wallach, *Liebigs Ann.* **237**, 251 (1887).

chloride and dimethylamine; b.p. 81·5–82·5° (23 mm). Chloroform (100·5 g, 0·84 mole), in benzene solution, was added, with stirring, to the cooled reaction mixture. When addition of the chloroform solution was complete, the dark reaction mixture was allowed to warm to room temp and was stirred for an additional hour. The mixture was extracted with 200 ml water and the aqueous layers backwashed with ether. The ether–benzene solution was dried with magnesium sulfate. The dark solution was concentrated *in vacuo*. The thick, dark oil obtained was transferred to an evaporative still and all volatile material collected. The final stages of this distillation were characterized by the sublimation of a pale yellow solid. The gas phase chromatogram of the distillate showed the presence of two major components and several minor components. One of the major components had a retention time identical to that for authentic dibenzyl. Its NMR spectrum and infrared spectrum were identical to those for authentic dibenzyl. A sample of the material obtained by gas phase chromatography was resublimed; m.p. and mixed m.p. 53·5°. Yield was 2·34 g (12·2%), from gas chromatogram peak area. The second major component had retention time identical to that for authentic N,N-dimethylphenylacetamide. The infrared spectrum of this component was superimposable with that of authentic N,N-dimethylphenylacetamide. A sample of this material was recrystallized from ether at low temperature. It had m.p. and mixed m.p. 38–40° (Kofler block). Yield was 1·1 g (3·19%), from gas chromatogram peak area. All efforts to separate the mixture of minor components present by gas chromatography and distillation were fruitless. None was present in isolable quantity.

The authentic N,N-dimethylphenylacetamide was prepared from the reaction of the acid chloride and dimethylamine. To 4·0 g (0·029 mole) phenylacetic acid was added 25 ml (41·5 g, 0·35 mole) thionyl chloride. The mixture was refluxed for 4 hr and then poured cautiously into an ice-cold solution of dimethylamine in water. The solution was made basic with aqueous sodium hydroxide. It was extracted with ether and the ether solution dried with magnesium sulfate. The ether was distilled off to give a yellow oil. The product was purified by gas phase chromatography and by three recrystallizations from ether at low temp, m.p. 38–40°.

Reaction of trimethylamine, chloroform, and potassium t-butylate. A slurry was prepared from 300 ml benzene and alcohol-free potassium t-butylate (from 35·2 g, 0·9 mole potassium metal) and cooled to ca. −10°. Trimethylamine (13·3 g, 0·23 mole) was added and the stirred mixture treated, dropwise, with a solution of chloroform (107·5 g, 0·9 mole) in benzene. When addition of the chloroform solution was complete the dark brown reaction mixture was allowed to warm to room temp and stirred for an additional 0·5 hr. The reaction mixture was extracted with water and the aqueous layers backwashed with ether.

After drying with magnesium sulfate the solution was concentrated *in vacuo*. The thick dark residue was transferred to an evaporative still and all volatile material removed *in vacuo*. During the final stages of this distillation there was considerable fuming in the still and a solid material (A) formed on the still cold finger. A portion of the distillate was transferred to a Piros–Glover Spinning band column and redistilled. After removal of benzene and t-butyl alcohol, a colorless liquid distilled at 50·5° (16 mm). Total yield was 2·32 g (5·73%, includes small amount of this material present as hydrochloride). When this distillation was attempted at atm press. complete decomposition of the product occurred. The distillate had a sweet, pleasant odor and lost HCl slowly on standing. I.R. (CS_2) 3·56 (m), 7·1(s), 8·75(m), 9·11(m), 9·39(s), 9·81(m), 10·19(s), 11·64(m), 12·90–13·00(s), 14·10–14·15(s). The NMR spectrum of this liquid had a sharp peak at 7·42 and one at 6·74 in an approximate 3:1 ratio, respectively.

When a benzene solution of 0·201 g (0·00114 mole) of this liquid product was treated with an aqueous solution of silver nitrate (5·81 g, 0·0342 mole) an immediate, copious white precipitate was produced. The reaction mixture was stirred at room temp (magnetic stirrer) for 0·5 hr. The benzene layer was separated off and the aqueous layer extracted 3 times with ether. The organic layers were combined and concentrated by distillation on the steam bath. The residue which contained a strong skin irritant was analyzed by gas phase chromatography. In addition to solvent peaks the residue showed the presence of one major component which had a retention time identical to that of N,N-dimethyl-α-chloroacetamide. The infrared spectrum of this product was superimposable with that of authentic N,N-dimethyl-α-chloroacetamide. Yield of the amide from gas chromatogram peak area was 0·072 g (52%).

The liquid product gave a picrate of *α,α,β-trichloroethyldimethylamine*, m.p., 134–136°. (Found: C, 29·6; H, 2·73; N, 13·8; Cl, 26·2. $C_{10}H_{11}N_4Cl_3O_7$ requires: C, 29·8; H, 2·97; N, 13·9; Cl, 25·9%).

The solid material (A) which sublimed during the course of the evaporative distillation was

resublimed 3 times to give almost white crystals which turned brown upon standing. The crystalline solid decomposed at 185°, with discoloration beginning at 170° (Hershberg appartus used with bath heated to 150° before insertion of sample). When treated with aqueous sodium hydroxide this solid gave a liquid whose infrared spectrum was identical to that of the liquid product. In addition a small amount of an amide (shown by infrared analysis) was produced in the base treatment.

The authentic N,N-dimethyl-α-chloroacetamide was prepared from the reaction of chloroacetyl chloride and dimethylamine. To 24·2 g (0·25 mole) α-chloroacetic acid was added 18·1 ml (30·0 g, 0·25 mole) thionyl chloride and the mixture refluxed for 1·5 hr. The resulting reaction mixture was allowed to cool and dissolved in 100 ml anhydrous ether. This solution was added, dropwise, with stirring, to a solution of 33·3 ml (22·5 g, 0·5 mole) dimethylamine in 100 ml anhydrous ether at −20°. When addition was complete the reaction was allowed to warm to room temp and stirred for an additional hour. The reaction mixture was extracted with dil, aqueous HCl. The ether layer was then extracted with dil, aqueous NaOH. The resulting ether solution was dried with magnesium sulfate. The ether was distilled off on the steam bath to give a yellow oil. This oil was distilled *in vacuo* to give 9·0 g (29%) of N,N-dimethyl-α-chloroacetamide, b.p. 71° (2 mm), lit.[43] b.p. 98·5–99·5° (11 mm). The product was a strong skin irritant.

An attempt to obtain α,α,β-trichloroethyldimethylamine by treatment of authentic N,N-dimethyl-α-chloroacetamide with phosphorous pentachloride gave no isolable product. To 0·28 g (0·0023 mole) N,N-dimethyl-α-chloroacetamide in 30 ml benzene was added 0·97 g (0·005 mole) phosphorous pentachloride. The reaction mixture was refluxed for 1·5 hr during which time it gradually darkened, finally becoming dark brown. The reaction mixture was allowed to cool and was then poured over cracked ice. The acidic reaction mixture was extracted with ether and then made basic with aqueous sodium hydroxide and reextracted. The ether solutions were dried with magnesium sulfate and the ether evaporated off. Both fractions gave a dark brown oil. Gas phase chromatograms of these oils showed only solvent peaks.

[43] W. A. Jacons and M Heidelberger, *J. Biol. Chem.* **21**, 148 (1915).

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FURTHER ASPECTS OF THE CHEMISTRY OF CIGARETTE SMOKE—II*

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Abstract—By vapour phase chromatography it has been shown that the acids in cigarette smoke simpler than lauric contain both even and odd numbers of carbon atoms, and the C_8, C_9 and C_{11} unsaturated acids also appear to be present. A new weak base has been separated from the hydrochloric acid extract of the smoke. From the neutral fraction (M_N of Paper I) a number of compounds have been isolated by chromatography one of which is low melting and appears to be $C_{29}H_{46}O$

IN Part I, Table 1 records the results obtained in a preliminary examination of the smoke from eight different brands of cigarettes and Table 2 the analysis of the methyl esters of the simpler acids in the very complex acid mixture in the smoke. Of the total of these simpler acids 30 per cent contain at least 15 acids simpler than lauric, with saturated and unsaturated members present to about the same extent. In view of the possible important role the acids might play,[1] this 30 per cent fraction has been further analysed, through the kindness of Dr. R. V. Crawford† and shown to be more complex than was suggested earlier.

The bases in cigarette smoke. In addition to those already recorded the hydrochloric acid extract obtained after acetic acid has removed the more strongly basic compounds contains a significant amount of a base whose I.R. absorption spectrum suggests the presence of a lactam group, and which does not appear to have been mentioned previously. A curious point found in working up this material is that successive treatments with hydrochloric acid eliminated small amounts of a neutral material whose properties and analysis agreed with hentriacontane (H.T.C.) although this does not form a complex with nicotine itself.

M_N. This fraction (Part I, Table 1) contains the neutral compounds including the hydrocarbons and the nitrogenous materials not removed by hydrochloric acid, or potassium in an inert solvent but are removed by lithium aluminium hydride. Although M_N contains a *very small* proportion of aromatic hydrocarbons much work has been done in recent years on the isolation and identification of any member with known carcinogenic action and especially of 3:4-benzpyrene. From spectrographic evidence this compound appears to be present to the extent of about 1 p.p.m.[2] and its presence appears to have been confirmed since Wynder and Hoffman state that two crystals of the compound were obtained by the sublimation of the product from 200 paper chromatograms.‡ The M_N fraction as a whole appears to be markedly terpenoid including steroid in character and only a slight separation can be effected

* Part I: G. R. Clemo, *Tetrahedron* 3, 168 (1958).
† Research Dept., J. Bibby and Sons Ltd.
‡ *London Symposium* July (1959).

[1] *J. Roy. Soc. Health* **79**, 74 (1959).
[2] H. R. Bentley and J. G. Burgan, *Analyst* **83**, 442 (1958).

by distillation in a molecular still at 10^{-4} mm. A more complete separation results from chromatography on alumina giving products whose analyses indicate a $C_{15}H_{24}$ compound with two double bonds, which is thus bicyclic and a $C_{20}H_{32}$ compound. Neither of these combines with maleic anhydride or has so far given a crystalline bromide. An interesting constituent is a low melting compound indicated by analysis to be $C_{29}H_{36}O$ with 5 double bonds, (although $C_{30}H_{48}O$ is not ruled out). It is, therefore, probably monocyclic. Rather surprisingly it gives no test for unsaturation with tetranitromethane but gives a light brown colour in acetic anhydride and sulphuric acid which changes after about 3 hours to a dull purple suggestive of a sterol. It is unchanged by refluxing with acetic anhydride alone (or in pyridine) and gives no oxime. Its I.R. absorption spectrum shows no evidence for carbonyl or conjugation, but for a hydroxyl group of uncertain type. This compound comes off the alumina column just before the sterols of which β- and γ-sitosterol and stigmasterol have been recorded as present recently by other workers.

There is some uncertainty in the literature about the melting points, specific rotations and solvent of crystallization of both β- and γ-sitosterol and whilst some workers give 137° as the m.p. of the β-compound, others state that it forms crystals with $\frac{1}{2}$ H_2O with a m.p. of 137·5°. The information on γ-sitosterol appears even less definite, but it appears to melt at 147–148°, although plates with 1 H_2O are also stated to melt at 147–148°. According to Heilbron *et al.*[3] two fully reduced stigmasterols, exist one of m.p. 127°, giving an acetate of m.p. 123°. From the sterol fractions coming off the column it is easy to obtain highly crystalline specimens melting at 137° and 147–148° which would appear to be β- and γ-sitosterol respectively, and whilst the I.R. absorption spectrum of the substance melting at 137° agrees substantially with that of β-sitosterol both spectra show peaks at 970 cm^{-1} which are characteristic of the C 22–23 side chain double bond of stigmasterol. This would also explain the low specific rotations found for the 137° and 147–148° materials e.g. $[\alpha]_D$, −46° for the 137° melting material (literature value of −37°). It is stated[4] that the side chain double bond of stigmasteryl acetate is selectively reduced over palladized charcoal in ethyl acetate to give β-sitosterol acetate and it was hoped to be able thus to eliminate the stigmasterol from the mixture coming off the column and thereby obtain pure β- and γ-sitosterols. When this experiment was kindly carried out by Dr. F. J. McQuillin the analysis of the resulting product indicated a reduction to stigmastanol and the I.R. absorption spectrum showed differences from that of β-sitosterol, but no material is available for a direct comparison. Some of the compounds described above were first recorded in an interim report to a committee of the Medical Research Council in 1956.

Although the M_N fraction from all the brands of cigarettes mentioned in Table 1 (*loc. cit.*) have not been examined in detail it can be stated that all the compounds described above have been obtained from the U.S., Russian, German, and French cigarettes referred to. Further, in view of the great increase in the use of tipped cigarettes it was of interest to examine whether the smoke from such tipped cigarettes differed substantially from the smoke issuing when the tips were removed. Although only two brands of popular tipped cigarettes have been so far examined it has been found that the tips effect approximately a 7 per cent reduction in the amount of M_N

[3] Heilbron, Jones, Roberts and Wilkinson, *J. Chem. Soc.* 344 (1941).
[4] Bernstein and Wallis, *J. Org. Chem.* **2**, 341 (1938).

(per 100 g of tobacco) and that all the neutral compounds described above can be isolated from the smoke of the tipped cigarettes. It is of course possible that the tips selectively remove some injurious material not so far identified.

EXPERIMENTAL

All carbon–hydrogen analyses and M.Ws are by Drs. Weiler and Strauss (Oxford) the oxygen determinations and most of the double bond estimations have been kindly carried out by Miss J. Cuckney (Imperial College) the rotations by Dr. F. J. McQuillin.

Methyl esters. The ether soluble free acid and phenolic mixture (15 g) was steam distilled giving 2·33 g of product and leaving non-volatile materials—including all hydroxy and di-carboxylic acids, of which 11·6 g was ether soluble and 0·36 g ether insoluble (evidence for the presence of unstable compounds). The 2·33 g in ether was thoroughly extracted with sodium carbonate solution and thus separated into phenols (1·61 g) and acids (0·51 g). The latter were esterified ($MeOH + H_2SO_4$) and on working up the product 0·22 g of esters boiled between 45°–80°/2 mm ($n^{20} = 1{\cdot}4878$). This 0·22 g was reduced in methanol with PtO_2/H_2 (6 cc absorbed in the first hour and 7 cc altogether) giving a pale yellow oil, b.p. 90–140°/20 mm $n^{20} = 1{\cdot}4846$. This simplified ester mixture has been shown by an efficient Reoplex vapour-phase column to contain at least 25 different esters. The amounts present from even numbered carbon atoms is rather small (nC_{14}, 2%; nC_{12}, 2%; nC_{10}, 5%; nC_8, 5%). A comparison of the curves given by the ester mixture before and after reduction shows an increase in the C_8, C_9 and C_{11} acid ester content after reduction, thus pointing to the unreduced mixture containing unsaturated C_8, C_9 and C_{11} components.

The HCl extracted basic mixture. When 1·45 g of this mixture was steam distilled 0·27 g of a yellow sweet smelling oil passed over. After treatment with sodium nitrite the material was again steam distilled, dissolved in hydrochloric acid, and freed from traces of non-basic material by extraction twice with ether—a yellow mobile oil (0·15 g b.p. 85°/2 mm) being obtained. (Found: C, 79·1, 78·8; H, 7·55, 7·6; N, 9·2, 9·3, 8·4. $C_{19}H_{22}ON_2$ requires: C, 77·5; H, 7·5; N, 9·5; $C_{20}H_{22}ON_2$, C, 78·8; H, 7·2; N, 9·1%). No reliable M.W. values or a crystalline picrate or picrolonate have been obtained. I.R. absorption bands 1700, 1450 and 750 cm^{-1} suggest the presence of >N·CO, >NMe and phenyl groups. The above non-basic material gave soft prisms from benzene–alcohol, m.p. 65° not depressed by admixture with H.T.C. (Found; C, 85·7; H, 13·9; Calc. for $C_{21}H_{44}$: C, 85·3; H, 14·7%).

M$_3$. When the neutral fraction is steam distilled 6–7% passes over as a mobile camphoraceous oil (b.p. 75°/2 mm M.W. about 170). It gives the $C(NO_2)_4$ test for unsaturation and catalytic reduction indicates the presence of one double bond but so far no crystalline derivative has been obtained. The steam non-volatile material, dissolved in light petroleum (10 cc, b.p. 60–80°), deposits on standing an amorphous solid (0·035 g) from which no pure substance has been obtained. The light petroleum soluble material (2·07 g) in a molecular still (10^{-4} mm) gave 0·3 g up to 100°, 0·15 g 100–150° and 0·68 g 150–250°, leaving 0·89 g of residue. From the first fraction materials corresponding to *a* and *b* below can be obtained but nothing definite from the remainder or residue.

Separation on alumina. Four separate lots of 1 g of the light petroleum soluble material in light petroleum (10 cc) were chromatographed on 20 × 0·8 cm columns of alumina, giving *a* (0·5 g, not adsorbed). Five elutions with light petroleum (10 cc) gave *b* (1·4 g) from the first washing and *c* (0·5 g) from the second to fifth (orange coloured) washings. Five elutions with light petroleum (10 cc) containing 10% benzene gave *d* (0·255 g), five elutions with 50% benzene–light petroleum mixture e_1 (0·1 g) from the first, and e_2 (0·3 g) from the second to fifth elutions. Five further elutions with benzene (10 cc) gave *f* (0·28 g), five with benzene containing 10% ether *g* (0·29 g), five with ether, *h* (0·35 g), five with benzene containing 10% ethanol *i* (0·1 g), and finally ethanol containing 10% acetic acid eluted *j* (0·08 g, benzene soluble). All weights after evaporation included the weight of traces of porous pot.

Fraction a. When dissolved in a small volume of acetone a trace of H.T.C. separated and by chromatographing the soluble material in light petroleum on alumina a colourless peppery smelling oil was obtained which nearly all distilled at 80°/2 mm approx (Found: C, 87·8; 87·7; H, 11·8; 12·1. M, 199. $C_{15}H_{24}$ requires: C, 88·2; H, 11·8; M. 204). The oil showed marked unsaturation with tetranitromethane and catalytic reduction indicated the presence of two double bonds. (Found: C, 86·4; H, 13·0. $C_{15}H_{28}$ requires: C, 86·5; H, 13·5%).

Fraction b. When treated as for *a* gave a thick oil, b.p. 130°/2 mm approx (Found: C, 87·8, 87·8; H, 11·9, 11·7; M, 278, 286: $C_{20}H_{32}$ requires: C, 88·2; H, 11·8%; M, 272.).

Fractions c. On standing some months in winter this solidified and when extracted with methanol gave 0·17 g of nearly white prisms, m.p.25–27°, raised to 27° by one further crystallization. The melt after solidification usually had m.p. 35°–36°. (Found: C, 84·8; H, 11·2; O, 3·63; M, 402, 400; $C_{29}H_{46}O$ requires: C, 84·9; H, 11·2; O, 3·9%; M, 410 $C_{30}H_{46}O$ requires: C, 84·9; H, 11·3; O, 3·8%, M, 423). The compound had only a small, if any specific rotation $[\alpha]_D$ −1·2° and in a catalytic reduction 9·299 mg absorbed 2·593 ml H_2 at N.T.P. which on the basis of $C_{29}H_{46}O$ indicated five double bonds.

Fractions d and e. These were chromatographed over alumina and only more of the above compound was obtained.

Fraction e_2. This material in light petroleum was adsorbed on a 10 × 0·8 cm alumina column and washed successively with 10 lots of light petroleum (10 cc), 5 lots of light petroleum containing 10% benzene, and in 5 lots of benzene–light petroleum mixture when all the material was recovered. The first material eluted gave a trace of a soft crystalline solid but that from the 2nd to 15th washings only gums. A brown band was eluted in the 16th and 17th washings (0·13 g) which gave colourless prisms m.p. 130° from methanol.

Fraction f. This 0·28 g crystallized easily from light petroleum, so it was dissolved in light petroleum containing 10% benzene and then chromatographed as under e_2. In this case 10% ether in benzene and finally 10% ethanol in benzene were needed to elute the last trace of material, but nothing definite could be isolated from these eluates. The last runnings with the 10% benzene gave 15 mg, m.p. 128–130°—once crystallized from methanol, whilst the 50% benzene runnings gave fractions of 0·06 g, 0·025 g and 0·05 g all of which were sparingly soluble in, and crystallized well from, methanol giving products: m.p.132°–136°, 135°–137° and 145°–148° respectively. All the above crystalline fractions gave the usual sterol colour reactions and on recrystallization the 135–137° material melted at 137° and the 145°–148° gave striking prisms m.p.148° (Found for the 137° material: C, 83·94, H, 12·1; and for the 148° material C, 83·5; H, 11·7. $C_{29}H_{50}O$ requires: C, 84·0; H, 12·1%).

Acetylation and reduction. 0·1 g of the combined crystalline fractions when refluxed with acetic anhydride gave 0·09 g of colourless plates, m.p.125°. When 83·3 mg were reduced in ethyl acetate (10 cc) with palladized charcoal/hydrogen, 4·6 cc hydrogen were absorbed at 20°, corresponding to 1·05 moles. H_2 per mole. The reduced product crystallized from methanol in prisms, m.p.125° and after hydrolysis with methanolic potassium hydroxide 37 mg of prisms were obtained from acetone, m.p.127°. (Found: C, 82·0; H, 12·7; $C_{29}H_{52}O$ requires: C, 83·6; H, 12·5%).

Fractions *g*, *h*, *i* and *j* have so far given only indefinite results.

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ARYL TELLURIUM TRIHALIDES—I

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Abstract—New aryl tellurium trichlorides have been prepared. A method for synthesizing aryl tellurium tribromides and triiodides based on the halogenolysis of the corresponding ditellurides is presented. Thiophenoxtellurine was obtained from *o*-thiophenoxyphenyltellurium trichloride.

ARYL tellurium trichlorides (III) were prepared by Morgan *et al.*[1-3] by the action of tellurium tetrachloride on aromatic compounds having an activated *para* position.

$$\underset{\text{I}}{\text{Ar—H}} + \underset{\text{II}}{\text{TeX}_4} \longrightarrow \text{HX} + \underset{\text{III}}{\text{ArTeX}_3}$$

$$\text{X} = \text{Cl}$$

This method was used later by Reichel and Kirschbaum[4] for preparing compounds of type III and by Reichel and Ilberg[5] who synthesized tellurium trichlorides derived from quinoline. Campbell and Turner[6] developed a method based on the reaction of organic mercury compounds with tellurium tetrachloride in dioxane.

$$\underset{\text{IV}}{\text{Ar—Hg—X}} + \underset{\text{II}}{\text{TeX}_4} \xrightarrow{\text{diox}} \underset{\text{III}}{\text{ArTeX}_3} + \text{HgX}_2 \cdot \text{dioxane}$$

$$\text{X} = \text{Cl}$$

The advantage of this procedure used by Farrar[7] and by Rheinboldt and Vicentini[8], permits the use of aromatic compounds without activated *para* positions.

In this work several aryl tellurium trichlorides including three new ones (III: Ar = *p*-C_6H_5—S—C_6H_4, 1-$C_{10}H_7$, XI; Table 1) were prepared.

These compounds were reduced with sodium sulphide in accordance with Reichel and Kirschbaum[9] giving rise to the corresponding diaryl ditellurides (V) (Table 1).

$$\underset{\text{III}}{2\ \text{ArTeCl}_3} \xrightarrow{\text{Na}_2\text{S}.9\text{H}_2\text{O}} \underset{\text{V}}{\text{Ar—Te—Te—Ar}}$$

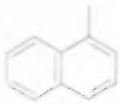
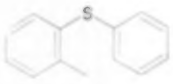
The preparation of di-*p*-hydroxyphenylditelluride (V: Ar = *p*-HO—C_6H_4) was not possible due to decomposition with separation of tellurium. The use of mild reducing agents led to the same results.

* Present address: Escola Politécnica da U.S.P. Praça Cel. Fernando Prestes, 74 São Paulo, Brasil. The experimental part of this work was executed in 1953, being part of the thesis oriented by the late Prof. H. Rheinboldt.

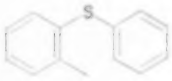
[1] G. T. Morgan and H. D. K. Drew, *J. Chem. Soc.* 2307 (1925).
[2] G. T. Morgan and R. E. Kellett, *J. Chem. Soc.* 1080 (1926).
[3] M. D. K. Drew, *J. Chem. Soc.* 233 (1926).
[4] L. Reichel and E. Kirschbaum, *Liebigs Am.* **523**, 211 (1936).
[5] L. Reichel and K. Ilberg, *Ber. Dtsch. Chem. Ges.* **76**, 1108 (1943).
[6] I. G. M. Campbell and E. Turner, *J. Chem. Soc.* 39 (1938).
[7] W. V. Farrar, *Research* **4**, 177 (1951); *Chem. Abstr.* **45**, 7543 (1951).
[8] H. Rheinboldt and G. Vicentini, *Chem. Ber.* **89**, 624 (1956).
[9] L. Reichel and E. Kirschbaum, *Ber. Dtsch. Chem. Ges.* **76**, 1105 (1943).

Very little is known of the aryl tellurium tribromides. Morgan *et al.*[2,3] described incompletely two tribromides while Vicentini *et al.*[10] prepared 2-naphtyltellurium tribromide (III: Ar = 2-$C_{10}H_7$: X = Br).

TABLE 1. ARYL TELLURIUM TRICHLORIDES: $ArTeCl_3$

Compound: Ar =	M.p.	Appearance	Analyses Te%	
			Calc.	Found
	164·5–165·5° (dec)	dark yellow needles from glacial acetic acid	30·44	30·60
	175–180° (dec)	yellow crystals from glacial acetic acid	35·33	35·14
	213–215°	yellow needles from glacial acetic acid	30·44	30·40

DIARYL DITELLURIDES: ArTeTeAr

Compound: Ar =	M.p.	Appearance	Analyses Te%	
			Calc.	Found
	89–90°	red needles from petroleum ether (50–70°)	40·78	40·41
	123·5–124·5	red needles from petroleum ether (50–70°)	50·08	49·82
	130·5–131°	orange red needles from petroleum ether (50–70°)	40·78	40·71

Aryl tellurium triiodides were unknown until the present. The synthesis of these compounds using tellurium tetrabromide and tellurium tetraiodide is not recommended due to the low reactivity of these tellurium tetrahalides.* The preparation of tribromides and triiodides by halogenolysis of the ditellurides (V) proceeds without difficulty and in quantitative yield (Tables 2 and 3).

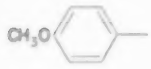
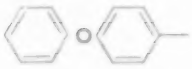
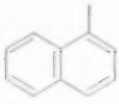
$$V + 3X_2 \longrightarrow \underset{III}{2ArTeX_3}$$

X = Br, I

* H. Rheinboldt. Private communication.

[10] G. Vicentini, E. Giesbrecht and L. R. M. Pitombo, *Chem. Ber.* **92**, 40 (1959).

TABLE 2. ARYL TELLURIUM TRIBROMIDES
Ar—$TeBr_3$

Compound: Ar =	M.p.	Appearance	Analyses Te%	
			Calc.	Found
	188–190° (dec)	yellow needles from acetic acid	26·89	26·81
	195–205° (dec)	yellow plates from acetic acid	26·12	26·53
	206·5–207°	yellow orange plates from acetic acid	23·78	23·61
	206–207°	yellow orange plates from acetic acid or benzene–petroleum ether (50–70°)	23·09	23·11
	159–160° (dec)	red orange needles from benzene–petroleum ether (50–70°)	25·80	25·85

In this connexion it is interesting to point out that the halogenolysis of the diaryl diselenides gives rise to aryl selenium trihalides[11] and to aryl selenenyl halides[12] depending on the molar proportion of the halogen used:

$$ArSeSeAr + 3X_2 \longrightarrow \underset{VII}{2ArSeX_3} \qquad X = Cl,Br$$

$$\underset{VI}{ArSeSeAr} + X_2 \longrightarrow \underset{VIII}{2ArSeX}$$

Aryl selenium trihalides are not stable, and can give rise to aryl selenenyl halides by loss of halogen:[13]

$$ArSeX_3 \longrightarrow ArSeX + X_2$$

The attempt to prepare the tellurenyl halides by the controlled halogenolysis of diaryl ditellurides (1 mole of ditelluride : 1 mole of halogen) was not successful, indefinite compounds being obtained,* with the exception of 2-naphtyltellurenyl iodide, prepared in pure and crystalline form.[10]

* H. Rheinboldt. Private communication.

[11] Houben-Weyl, *Methoden der Organ. Chemie* (IVth Ed.) pp. 1130, 1132. Georg Thieme Verlag, Stuttgart (1955).

[12] Houben-Weyl, *Methoden der Organ. Chemie* (IVth Ed.) pp. 1161, 1164. Georg Thieme Verlag, Stuttgart (1955).

[13] Houben-Weyl, *Methoden der Organ. Chemie* (IVth Ed.) pp. 1162, 1166. Georg Thieme Verlag, Stuttgart (1955).

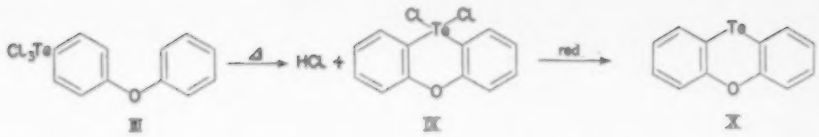
TABLE 3. ARYL TELLURIUM TRIIODIDES
$ArTeI_3$

Compound: Ar =	M.p.	Appearance	Analyses Te%	
			Calc.	Found
	131–133° (dec)	small black crystals from benzene	20·73	21·04
	133–134° (dec)	black needles from benzene	20·27	20·27
	160·5–161° (dec)	red-black plates from benzene–petroleum ether (50–70°)	18·83	18·84
	125–150° (dec)	small dark-red brilliant crystals from water–sulphuric acid	21·21	21·18
	180° (dec)	small dark red crystals from benzene–petroleum ether (50–70°)	18·39	18·52
	133° (dec)	black brilliant needles from benzene–petroleum ether (50–70°)	20·07	20·07

The preparation of *p*-hydroxyphenyltellurium tribromide and triiodide by this method is impossible due to the nonexistence of the corresponding ditelluride. Meanwhile the triiodide (III: Ar = *p*-HO—C_6H_4; X = I) was prepared by the reaction of the corresponding trichloride with a solution of potassium iodide.

This reaction fails when potassium bromide is used, the starting material being recovered unchanged.

Drew[3] found that by heating *p*-phenoxyphenyltellurium trichloride (III: Ar = *p*-C_6H_5—O—C_6H_4) at a temperature above its melting point a cyclization involving rearrangement occurs, and 10,10-dichlorophenoxtellurine (IX) is formed. This compound was reduced to the phenoxtellurine (X).



When *p*-thiophenoxyphenyl tellurium trichloride (III: Ar = *p*-C_6H_5—S—C_6H_4) was similarly treated with the purpose of obtaining 10,10-dichlorothiophenoxtellurine (XII), decomposition occurred. This cyclic sulphur tellurium compound was prepared starting from the *ortho* derivative (XI).

By reduction of XII with sodium sulphide thiophenoxtellurine (XIII) was obtained in very good yield.

A similar reaction is shown by *o*-biphenylylselenium trichloride (XIV)

EXPERIMENTAL

Trichlorides

p-*Thiophenoxyphenyltellurium trichloride* (III: Ar = *p*-C_6H_5—S—C_6H_4). A solution of 9·3 g (0·05 mole) diphenyl sulphide and 13·5 g (0·05 mole) tellurium tetrachloride in 20 cc chloroform was refluxed for 40 hr, an evolution of hydrogen chloride being noted. The dark crystalline product was dissolved in benzene and precipitated with petroleum ether (50–70°). Crude trichloride (8·8 g, 42% yield) was purified from glacial acetic acid or from a mixture of benzene and petroleum ether (50–70°) as dark yellow needles m.p. 164·5–165·5° (dec).

p-Methoxyphenyltellurium trichloride (III: Ar = *p*-CH_3—O—C_6H_4; m.p. 191–193°), *p*-ethoxyphenyltellurium trichloride (III: Ar = *p*-C_2H_5—O—C_6H_4; m.p. 179–180°), *p*-phenoxyphenyltellurium trichloride (III: Ar = *p*-C_6H_5—O—C_6H_4; m.p. 156–157°), and *p*-hydroxyphenyltellurium trichloride (III: Ar = *p*-HOC_6H_4; m.p. 223–227° (dec) were prepared in accordance with the procedure of Reichel and Kirschbaum[4] and Drew[9].

1-*Naphtyltellurium trichloride* (III: Ar = 1-$C_{10}H_7$). A solution of 7·2 g (0·02 mole) 1-naphtyl mercury chloride[14] and 5·4 g (0·02 mole) tellurium tetrachloride in 40 cc pure dioxane was refluxed for 2 hr. The dioxane mercury chloride complex that precipitates on cooling was removed by filtration. The dark yellow solution was concentrated to a viscous oil. On cooling and adding petroleum ether (50–70°) the oil solidified and was separated by filtration and dried on a porous plate. The crude trichloride (8·8 g) was contaminated with dioxane mercury chloride complex giving a 96% yield calculated on the ditelluride. Recrystallization from glacial acetic acid furnished yellow crystals m.p. 175–180° (dec).

[14] A. N. Nesmejanow, *Ber. Dtsch. Chem. Ges.* **62**, 1010 (1929).

o-Thiophenoxyphenyl mercury chloride. Sodium nitrite (12 g, 0·166 mole) was added to a mixture of 40 g (0·166 mole) *o*-thiophenoxyaniline hydrochloride, (prepared reducing 2-nitrodiphenyl sulphide with Fe/acetic acid; m.p. 36°) 75 cc conc hydrochloric acid and 80 g ice, keeping the temperature at 0–5°. To the filtrate was added, dropwise, with stirring, a solution of 45·1 g (0·166 mole) of mercury chloride in 100 cc cold hydrochloric acid (50%). During the addition the temperature must be maintained at 0°. An orange yellow precipitate formed and stirring was continued for 30 min. The product was filtered, washed with water, with alcohol and finally with ether, yielding the diazonium salt mercury chloride complex (75 g, 88·7%). A suspension of the complex in 270 cc acetone was cooled to —60°, treated with 18·2 g metallic copper (freshly prepared), and the temp. maintained at —60° for 12 hr and then slowly brought to normal temp. The brown product was filtered, extracted with acetone and the yellow solution allowed to crystallize, yielding 54·5% (33 g). Recrystallization from alcohol furnished colourless plates m.p. 135–136°. (Found S, 7·63. $C_{12}H_9ClHgS$ requires: S, 7·61%).

o-Thiophenoxyphenyltellurium trichloride (XI). Starting with 8·4 g (0·02 mole) of *o*-thiophenoxyphenyl mercury chloride and proceeding as in the case of 1-naphtyltellurium trichloride, 9·6 g crude trichloride contaminated with dioxane mercury chloride complex was obtained. The yield calculated on the basis of the ditelluride is 80·6%. Recrystallization from glacial acetic acid gave yellow needles m.p. 213–215°.

Aryl tellurium trichlorides solubilities. They are very soluble in cold methanol and ethanol, soluble in both glacial acetic acid and chloroform, sparingly soluble in benzene, insoluble in carbon tetrachloride and petroleum ether.

Ditellurides (Table 1)

Di-p-thiophenoxyphenylditelluride (V: Ar = p-$C_6H_5SC_6H_4$). *p*-Thiophenoxyphenyltellurium trichloride (0·42 g, 0·001 mole) was added to 3·6 g (0·015 mole) hydrated sodium sulphide (Na_2S—$9H_2O$) and heated at 95–100°. The reaction was exotermic and the di-*p*-thiophenoxyphenylditelluride separated as a red oil, the temp being maintained unchanged for 15 min. The mixture was then diluted with water, and on cooling the ditelluride separated out quantitatively.

In the same manner di-1-naphtylditelluride, di-*o*-thiophenoxyphenylditelluride (Table 1) and the known di-*p*-methoxyphenylditelluride[2,4] (m.p. 59–60°), di-*p*-ethoxyphenylditelluride[1,4] (m.p. 107°), di-*p*-phenoxyphenylditelluride[3] (m.p. 88–88·5) were prepared.

In the case of *p*-hydroxyphenyltellurium trichloride a decomposition occurred, forming tellurium. Sodium bisulphite, zinc in chloroform, hydrazine sulphate and phosphorous acid were all tried without success.

The diaryl ditellurides are soluble in cold benzene, chloroform and carbon tetrachloride, and in warm methanol, ethanol, glacial acetic acid and petroleum ether (50–70°).

Tribromides (Table 2)

p-*Methoxyphenyltellurium tribromide* (III: Ar = p-$CH_3OC_6H_4$). To a cold solution of 0·47 g (0·001 mole) di-*p*-methoxyph nylditelluride was added dropwise with stirring 0·48 g (0·003 mole) bromine dissolved in a few cc carbon tetrachloride. The *p*-methoxyphenyltellurium tribromide separated quantitatively as an orange solid.

In the same manner *p*-ethoxyphenyltellurium tribromide, *p*-phenoxyphenyltellurium tribromide, *p*-thiophenoxyphenyltellurium tribromide, 1-naphtyltellurium tribromide were prepared.

The *p*-hydroxyphenyltellurium trichloride treated with potassium bromide in benzene was recovered unchanged.

The tribromides show solubilities similar to the corresponding trichlorides.

Triiodides (Table 3)

p-*Methoxyphenyltellurium triiodide* (III: Ar = p-$CH_3OC_6H_4$). The procedure was similar to that used for the corresponding tribromides. The yields were quantitative with exception of *p*-methoxyphenyltellurium triiodide obtained in a 93% yield. The *p*-hydroxyphenyltellurium triiodide was prepared by treating a solution of the corresponding trichloride in methanol with excess aqueous potassium iodide.

The triiodides are sparingly soluble in the usual organic solvents but are soluble in diosane. An exception is *p*-hydroxyphenyltellurium triiodide which is soluble in water, methanol and ethanol.

10,10-*Dichlorothiophenoxtellurine* (XII). *o*-Thiophenoxyphenyltellurium trichloride (2·1 g, 0·005 mole) was heated at 240–250° in a glass tube with stirring for 30 min. Evolution of HCl was noted. On cooling, the dark liquid solidified to a dark yellow mass (1·9 g). This was dissolved in acetone, the solution filtered from a small residue of tellurium and crystallized, yielding needles (0·8 g, 42%), m.p. 265–270° (at 230°, a change in the crystalline form was noted). (Found Te, 33·24. $C_{12}H_6Cl_2STe$ requires: Te, 33·34%).

Thiophenoxtellurine (XIII). To 0·8 g (0·002 mole) of XII 7·2 g (0·03 mole) hydrated sodium sulphide was added and heated at 100° for 15 min. The reaction mixture was diluted with water and the product filtered and dried (0·6 g, 96%). Recrystallization from ethanol gave pale yellow needles m.p. 122–123·5°. (Found Te, 40·90. $C_{12}H_8STe$ requires: Te, 40·92%).

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THE CONVERSION OF PODOCARPIC ACID TO NIMBIOL[1]

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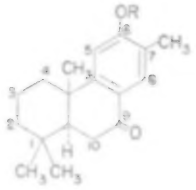
Abstract—Podocarpic acid has been unambiguously converted to nimbiol[2] and nimbiol methyl ether[2] thus confirming the complete structures assigned[3,4] to these substances. In the course of this work, a group of C-7 methyl derivatives of podocarpic acid has been prepared. The physical constants of these methyl derivatives are compared with the constants of the parent substances.

NIMBIOL, a compound isolated[2] from the trunk bark of *Melia azadirachta* Linn. has been assigned[3,4] the structure Ia.



Ia R=H

b R=CH_3

The pioneering work of Campbell and Todd[5] together with our own previous experience with the introduction of various substituents on the phenolic ring of podocarpic acid (C-7)[6] and with the introduction of a keto group at the carbon adjacent to the phenolic ring (C-9)[7] placed us in a favorable position to confirm the complete structure assigned[4] to nimbiol by Choudhuri *et al.*

Methyl O-methyl-7-carboxypodocarpate (II),[8] a compound readily available by the oxidation of methyl O-methyl-7-acetylpodocarpate,[5a,b] was reduced with lithium aluminum hydride in tetrahydrofuran to the diol III. The hydroxymethylene on the aromatic ring in III was smoothly converted to the desired methyl group by hydrogenolysis over palladium–charcoal in the presence of hydrochloric acid. It was anticipated that the conversion of the alcohol (IV) to the aldehyde (V) would be complicated by oxidation of the aldehyde to the acid and by the conversion of the C-9 methylene group to a keto group. From model experiments using O-methylpodocarpinol it was found that the C-1 hydroxymethylene group could be converted to the aldehyde most

[1] A preliminary report of this work has been published: R. H. Bible, Jr., *Tetrahedron Letters* No. 9, 20 (1960); E. Wenkert and V. I. Stenberg have recently reported on the partial synthesis of nimbiol: 137th National Meeting of the American Chemical Society, Cleveland, Ohio, April (1960); and M. Fetizon and J. Delobelle have reported on the synthesis of d,l-nimbiol methyl ether: *Tetrahedron Letters* No. 9, 16 (1960).
[2] P. Sengupta, S. N. Choudhuri and H. N. Khastgir, *Chem. & Ind.* 861 (1958).
[3] S. N. Choudhuri, H. N. Khastgir and P. Sengupta, *Chem. & Ind.* 634 (1959).
[4] S. N. Choudhuri, H. N. Khastgir and P. Sengupta, *Chem. & Ind.* 1284 (1959).
[5] [a] W. P. Campbell and D. Todd, *J. Amer. Chem. Soc.* **62**, 1287 (1940); [b] W. P. Campbell and D. Todd, *Ibid.* **64**, 928 (1942).
[6] [a] R. H. Bible, Jr., *J. Amer. Chem. Soc.* **79**, 3924 (1957); [b] U.S. Pat. 2,750,373 (1956).
[7] U.S. Pat. 2,705,725 (1955); U.S. Pat. 2,759,014 (1956); U.S. Pat. 2,854,474 (1958).
[8] U.S. Pat. 2,767,162 (1956).

conveniently by oxidation with chromic acid–sulfuric acid in acetone.[9] The alcohol (IV) was smoothly converted to the aldehyde (V) using these conditions. The work of Campbell and Todd[5b] indicated that the Wolff–Kishner reduction of this aldehyde through the semicarbazone (VI) would be accompanied by partial demethylation of the ether. In view of this anticipated demethylation, the crude reduction product (VII) was remethylated. In order to ascertain if a C-7 alkyl group would undergo oxidation

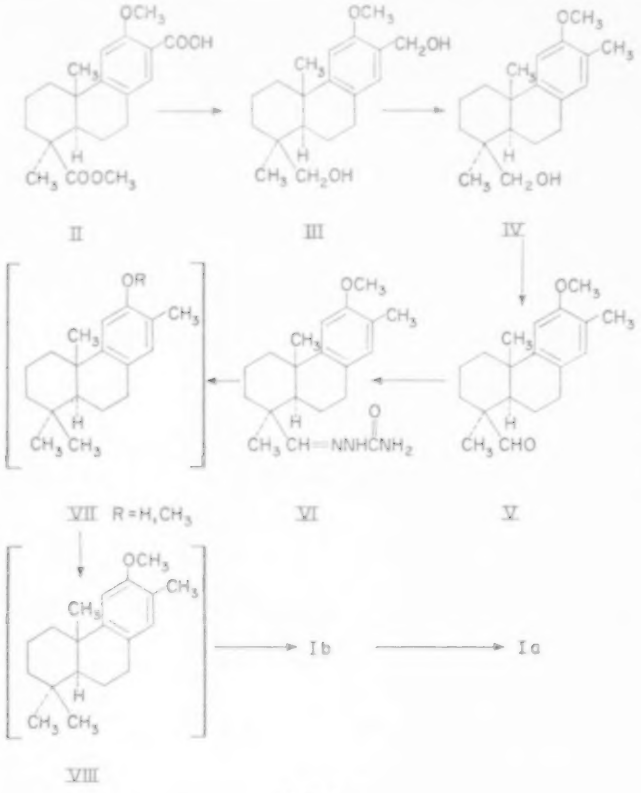


FIG. 1.

under conditions similar to those which we had previously employed[7] for the introduction of a C-9 keto group, methyl O-methyl-7-propylpodocarpate was subjected to these conditions. Methyl O-methyl-7-propyl-9-oxopodocarpate was obtained in good yield. Application of these oxidizing conditions to the crude remethylated Wolff–Kishner reduction product (VIII) gave an easily isolable crystalline solid having the structure Ib. This material was shown to be identical with nimbiol methyl ether by a comparison of physical constants (Table 1) and by a direct comparison of the substances (no depression of the melting point on admixture; identical infrared absorption spectra; identical ultraviolet spectra). Demethylation of the ether Ib with pyridine hydrochloride gave the corresponding free phenol Ia. The physical properties

[9] The use of this method was suggested by an observation made by Dr. Robert R. Burtner. The reagent was prepared by dissolving chromic acid (136.2 g) and conc sulfuric acid (110 ml) in water (total volume = 500 ml). See K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.* 39 (1946).

of this phenol (Table 2) were in good agreement with those reported for nimbiol; direct comparison (no depression of the melting point on admixture; identical infrared absorption spectra in KBr) proved that these two substances were identical. Remethylation of the phenol (Ia) gave the starting methyl ether (Ib).

This conversion of podocarpic acid to nimbiol thus confirms the complete structure assigned[4] to nimbiol by Choudhuri *et al.*

Our first approach to the synthesis of VI was by the Rosenmund reduction of the

Table 1. Comparison of Ib prepared from podocarpic acid with nimbiol methyl ether

Compound	m.p.	$[\alpha]_D^{CHCl_3}$	λ_{max}^{EtOH} mμ (ε)
Ib	142–144°	+43°	229·5 (15,000) 278·5 (13,900) 300 (shoulder)
Nimbiol methyl ether[4]	142–143°	+43·7°	229·5 (15,000)* 278·5 (14,000) 300 (shoulder)

* Our values obtained using a sample from Dr. P. Sengupta.

Table 2. Comparison of Ia prepared from podocarpic acid with nimbiol

Compound	m.p.	$[\alpha]_D^{CHCl_3}$	λ_{max} mμ (log ε)	
			EtOH	0·1 N NaOH/95% EtOH
Ia	248–252°	+33°	234 (4·13), 283 (4·10) 300 (shoulder)	253 (3·84), 345 (4·38)
Nimbiol[4]	244°	+32·2°	231 (4·07), 286 (4·06)	251 (3·89), 344 (4·33)

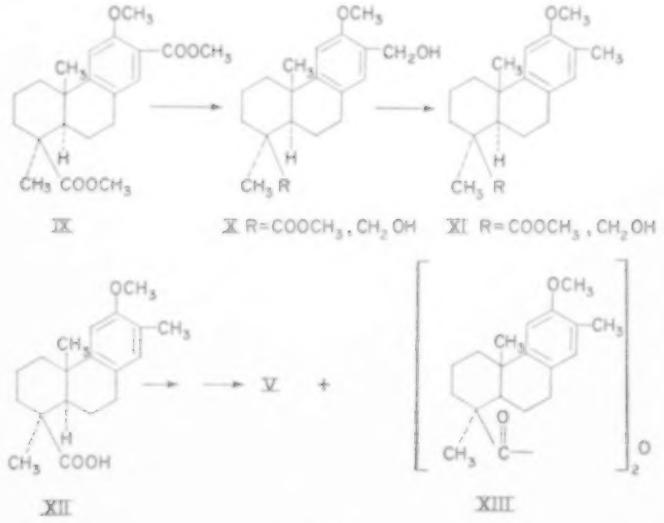
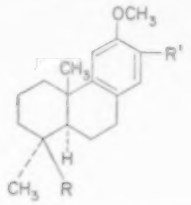


Fig. 2.

TABLE 3. COMPARISON OF C-7 METHYL DERIVATIVES OF PODOCARPIC ACID WITH THE CORRESPONDING PARENT COMPOUNDS



Compound	R	R′	m.p.	$[\alpha]_D^{CHCl_3}$*	λ_{max}^{MeOH} mμ (ε)*
O-Methylpodocarpinol[5b]	CH_2OH	H	90–91·5°	+67°	279 (2330) 286·5 (2080)
IV	CH_2OH	CH_3	83–85°	+68°	280 (2970) 287 (2830)
O-Methylpodocarpinal[5b]	CHO	H	133–135°	+87°	279 (2490) 286·7 (2250)
V	CHO	CH_3	110–111·5°	+87°	281 (3090) 286 (2990)
O-Methylpodocarpinal semicarbazone[5b]	$CH{=}NNHCNH_2$ (O)	H	205° (d)		278·5 (2570) 286·6 (2305)
VI	$CH{=}NNHCNH_2$ (O)	CH_3	210–212°		280 (3290) 286 (3060)
O-Methylpodocarpic acid[19]	COOH	H	158°	+132°	278·5 (2320) 286·5 (2106)
XII	COOH	CH_3	196·5–199·5°	+131°	280 (3020) 286·5 (2900)
Anhydride of O-methylpodocarpic acid	$(CO)_2O$	H	212·5–215°	+116°	278·5 (4650) 286·5 (4200)
XIII	$(CO)_2O$	CH_3	199·5–203°	+112°	

* The values given here for the known substances were obtained by us using samples prepared by the published procedures.

corresponding acid chloride. For this purpose the diester (IX) was allowed to react with lithium aluminum hydride in tetrahydrofuran at room temperature for a short time. It was anticipated that the highly hindered C-1 ester would not be reduced under these conditions.[10] Quite unexpectedly the hindered ester was reduced to a large extent. The resulting product (X) was hydrogenated to give the corresponding mixture (XI) of C-7 methyl derivatives. Hydrolysis of this mixture followed by purification of the acidic portion gave O-methyl-7-methylpodocarpic acid. The reduction of the acid chloride of XII gave the anhydride (XIII) along with the aldehyde

[10] H. H. Zeiss, C. E. Slimowicz and V. Z. Pasternak, *J. Amer. Chem. Soc.* **70**, 1981 (1948), found that podocarpic acid was reduced only very slowly (4·6% in 2 hr) by lithium aluminum hydride. Since these authors had used a 4 day reaction time for the reduction of methyl O-methylpodocarpate, we had assumed that the ester group was also reduced very slowly.

[19] I. R. Sherwood and W. F. Short, *J. Chem. Soc.* 1006 (1938).

(V) which was isolated as the semicarbazone (VI). This route was not as convenient as that shown in Fig. 1 for the preparation of a reasonable amount of VI.

During the course of this work a number of C-7 methyl derivatives of substances related to podocarpic acid became available. The physical properties of these homologs are summarized in Table 3. The introduction of the C-7 methyl group causes an increase in the molecular extinction coefficient of the ultraviolet absorption bands. Consistent differences can be detected in the infrared absorption spectra (Table 4). A number of these differences can be assigned to various effects on the aromatic ring[11]

Table 4. Consistent changes in the infrared absorption spectra brought about by the introduction of a C-7 methyl group in podocarpic acid derivatives (solutions in chloroform)*

These bands disappear:	7·77, 8·51 μ, and 12·38 $\pm$ 0·07 μ (KBr)
These bands appear:	8·76 and 9·96 μ†
The ratios of intensities of these bands decrease:	6·18, 6·34 (pair)‡/6·64 μ, 9·58/9·37 μ
This doublet becomes a single band:	7·89, 7·96 → 7·94 μ
The intensity of this band is increased:	11·72 μ

* Wave lengths of these bands have varied $\pm$0·03 μ.
† The anhydride of O-methylpodocarpic acid also has a strong band in this region.
‡ The semicarbazones have a complicating band at 6·37 μ.

[decrease in intensity of the in-plane skeletal vibration bands in the 6 μ region; disappearance of the out-of-plane hydrogen bending band (two adjacent hydrogens) at about 12·4 μ; increase in intensity of the 11·72 μ band (isolated hydrogens)] while others (doublet near 8 μ becomes a single band; decrease in intensity of the 9·58 μ band) can probably be attributed to the change in the environment of the methoxy group.[12]

EXPERIMENTAL[13]

Except where noted, rotations were determined using 0·5–1·20% chloroform solutions; infrared adsorption spectra were obtained using chloroform solutions; and ultraviolet adsorption spectra were run on methanol solutions. All melting points were taken on a Fisher–Johns block and were corrected using standard compounds.

Methyl O-methyl-7-carboxypodocarpate[8,14] (II). A solution of sodium hydroxide (72 g) in water (600 ml) was cooled to 3°. Bromine (36 ml) was added dropwise with stirring while the reaction mixture was maintained at 3–5° over a period of 45 min. The resulting mixture was stirred for an additional 15 min. A solution of methyl O-methyl-7-acetylpodocarpate[8a] (68·8 g) in t-butanol (1300 ml) was added to the reaction mixture at 4–6° over a period of 50 min. The reaction mixture was stirred at 3–5° for an additional 30 min followed by stirring at room temp overnight. A solution of sodium sulfite (83·4 g) in water (800 ml) was added to the reaction mixture. The solution was acidified with conc HCl and was then diluted with water to a total volume of 12 l. The solid was collected, washed with water, and then recrystallized twice from aqueous acetone (charcoal); 59·7 g; m.p. 169·5–170·5°; $[\alpha]_D$ +134°; λ_{max} 242 (ε 9410) and 302 mμ (ε 3420); 5·85 (broad) and 3·06μ

[11] L. J. Bellamy, *The Infrared Spectra of Complex Molecules* (2nd Ed.) p. 65. John Wiley, New York (1958).
[12] L. J. Bellamy, *The Infrared Spectra of Complex Molecules* (2nd Ed.) p. 115. John Wiley, New York (1958).
[13] All U.V. and I.R. spectra and rotations were performed by the Analytical Department of G. D. Searle and Company under the direction of Dr. R. T. Dillon. Elementary analyses were determined by the Analytical Department and by Micro-Tech, Skokie, Illinois.
[14] This oxidation was patterned after the method described [U.S. Pat. 2,769,822 (1956)] for progesterone.

(KBr). (Found: C, 69·51; H, 7·52. $C_{20}H_{26}O_5$ requires: C, 69·34; H, 7·57%). (Reported:[8] m.p. 164°.)

O-*Methyl-7-hydroxymethylpodocarpinol* (III). A solution of II (25·4 g) in tetrahydrofuran (150 ml) was added with stirring over a period of 27 min to a solution of lithium aluminum hydride (10 g) in tetrahydrofuran (200 ml). Within 30 min a large amount of white solid separated from the reaction mixture. An additional 100 ml of tetrahydrofuran was added. The reaction mixture was stirred and refluxed for 1·5 hr and was then allowed to stand at room temp for 16 hr. The reaction mixture was decomposed by the sucessive addition of a solution of water (11 ml) in tetrahydrofuran (100 ml), 20% (w/v–8 ml) aqueous sodium hydroxide, and water (37 ml). The white solid was filtered off and washed with tetrahydrofuran. The combined filtrates were diluted to a total volume of 6 l., with water. The resulting crystalline solid (19·3 g; m.p. 119·5–123°) was recrystallized from aqueous methanol (charcoal); $[\alpha]_D$ +69°; λ_{max} 280 (ϵ 2860); and 285 m μ (ϵ 2,850) 2·73 and 2·85 μ. (Found: C, 74·94; H, 9·19. $C_{19}H_{28}O_3$ requires: C, 74·96; H, 9·27%).

O-*Methyl-7-methylpodocarpinol*[15] (IV). A solution of the diol III (12 g) in 95% ethanol (100 ml) was shaken with 5% palladium–charcoal (3 g) in an atmosphere of hydrogen (35–60 lb/in²) at room temp for a total of 16·5 hr. The product was crystallized from aqueous methanol and the resulting solvated material was azeotroped dry with benzene. The residue was stirred with a small amount of hexane. This mixture was permitted to evaporate. The resulting crystalline solid amounted to 9·2 g; λ_{max} 2·75 and 2·85 μ (see Table 3). (Found: C, 79·11; H, 9·94. $C_{19}H_{28}O_2$ requires: C, 79·12; H, 9·79.)

O-*Methyl-7-methylpodocarpinal* (V). The alcohol IV (4·00 g) in acetone (25 ml) was oxidized with a standard chromic acid–sulfuric acid solution[9] (3·37 ml). The product was purified by the method used below for O-methylpodocarpinal. Two recrystallizations from aqueous acetone gave the desired aldehyde; 2·48 g; λ_{max} 3·62 and 5·79 μ. (See Table 3.) The sample for analysis was sublimed at 0·1 mm (Found: C, 79·44; H, 9·34. $C_{19}H_{26}O_2$ requires: C, 79·68; H, 9·15). A small amount of O-methyl-7-methylpodocarpic acid (XII) was obtained as a by-product in this oxidation.

Semicarbazone of O-*methyl-7-methylpodocarpinal* (VI). The aldehyde V (2·02 g) in pyridine (75 ml) was treated[16] with a solution of semicarbazide acetate (prepared from 4 g of semicarbazide hydrochloride and 4·0 g of sodium acetate) in 95% ethanol (40 ml). This solution was allowed to stand overnight and then was diluted with water. The crude product was washed with water and was then dried at 100° at 0·1 mm for 2 hr; 2·34 g; m.p. 200·5–211·5°. An analytical sample was obtained by two recrystallizations from aqueous methanol; λ_{max} 2·81, 2·86, 2·92, 2·96, 5·88 and 6·36 μ. (See Table 3.) (Found: C, 69·88; H, 8·38. $C_{20}H_{29}N_3O_2$ requires: C, 69·94; H, 8·51%).

6-*Methoxy-7-methyl-9-oxopodocarpane*[16] (Ib). The crude semicarbazone (2·34 g) was heated with a solution of sodium ethoxide in ethanol (prepared by dissolving 5 g of sodium in 50 ml of absolute ethanol) at 200–210° for 15 hr. The reaction mixture was diluted with water and ether. The ether layer was washed with water. The residue resulting from removal of the ether was dissolved in methanol and remethylated by treatment with 10% sodium hydroxide and dimethyl sulfate. The remethylated material was taken up in ether. The ether was washed with water. The residue remaining after removal of the ether was azeotroped dry with benzene, and then dissolved in acetic acid (50 ml). A slurry of chromic acid (0·650 g) in water (0·25 ml) and acetic acid (1·0 ml) was added slowly to the acetic acid solution. This reaction mixture was allowed to stand at room temp overnight. The reaction mixture was diluted with water and ether. The ether solution was washed with water, Claisen's alkali, and then with water. The ether was removed to give a crystalline residue. This material was recrystallized 4 times from aqueous methanol (charcoal); 0·71 g. This product was identical (no depression of the m.p. on admixture; identical infrared absorption spectrum at 5% in chloroform; identical ultraviolet spectra) with nimbiol methyl ether.[2] (See Table 1).

6-*Hydroxy-7-methyl-9-oxopodocarpane* (Ia). The ether Ib (0·30 g) was heated with pyridine hydrochloride (2·0 g) at 210° for 40 min. The reaction mixture was diluted with water. The product was collected, washed with water, recrystallized twice from aqueous methanol, and then sublimed (0·01 mm); 0·13 g; platelets. This product was identical [no depression of the m.p. on admixture; identical infrared absorption spectra (KBr)] with nimbiol.[2] (See Table 2.) Remethylation of the phenol with 10% NaOH and dimethyl sulfate gave the original methyl ether (Ib).

O-*Methylpodocarpinal*.[16] A standard chromic acid–sulfuric acid solution[9] (2·43 ml) was added

[15] We are indebted to M. G. Scaros for technical assistance in the hydrogenations and in the Wolff–Kishner reduction.

[16] This procedure was patterned after that described by Campbell and Todd[16b].

with stirring to a solution of O-methylpodocarpinol (2·74 g) in acetone (25 ml). The reaction was maintained at 15–26° during this addition. The reaction mixture was diluted with water and ether. The aqueous layer was separated and re-extracted twice with ether. The combined ether layers were washed successively with water, 10% aqueous sodium hydroxide, and then with water. Distillation of the ether gave a crystalline residue which was recrystallized from aqueous acetone to give the aldehyde; 2·02 g; m.p. 135–139·5°; λ_{max} 3·64 and 5·81 mμ (see Table 3).

A solution of O-methylpodocarpinol (2·74 g) in pyridine (30 ml) was added to a cold solution of chromic acid (1·55 g) in pyridine[17] (30 ml). The resulting mixture was allowed to stand overnight. The mixture was diluted with water and ether. After removal of the solid by filtration, the ether solution was washed with water, 2% sodium hydroxide, and finally with water. Removal of the solvent gave a residue which was recrystallized from aqueous acetone to give the aldehyde; 0·65 g; m.p. 132–136·5°.

A mixture of O-methylpodocarpinol (2·00 g), toluene (100 ml), cyclohexanone (32 ml), and 16·8 ml of a 25% (w/v) solution of aluminum isopropoxide in toluene was refluxed for 30 min. The cooled mixture was treated with a saturated solution of sodium potassium tartrate (100 ml). The organic layer was separated and washed with sodium potassium tartrate solution and then with water. The solvent and excess cyclohexanone were distilled under vacuum. The residue was dissolved in acetone. After removal of a small amount of insoluble material, the acetone solution was diluted at its b.p. with water until the solution was turbid. The crystalline material which precipitated on cooling was recrystallized 3 more times from aqueous acetone; 0·15 g; m.p. 131–136°.

Methyl O-*methyl-7-methoxycarbonylpodocarpate* (IX). The acid II was methylated by repeated treatment with 10% sodium hydroxide and dimethyl sulfate in methanol. The product was dissolved in ether. The ether solution was washed successively with water, 2% sodium hydroxide, and then with water. The ester was recrystallized from aqueous methanol; m.p. 141–143·5°; $[\alpha]_D$ +132°; λ_{max} 243 (ε 10,000) and 305 mμ (ε 3660); 5·78 μ (broad). (Found: C, 69·73; H, 7·78. $C_{21}H_{28}O_5$ requires: C, 69·97; H, 7·83%).

O-*Methyl-7-methylpodocarpic acid* (XII). The diester IX (20·0 g) was dissolved in ether (750 ml) and benzene (100 ml). This solution was added (45 min) to a mixture of lithium aluminum hydride (4 g) in ether (100 ml). An additional 100 ml of benzene was added to the mixture. The resulting slurry was stirred for 40 min at room temp. The excess lithium aluminum hydride was decomposed by the successive addition of ethyl acetate (100 ml), water (100 ml), and 10% HCl (200 ml). The organic layer was separated and washed with water, 2% HCl, and then with water until the washings were neutral. The solvents were distilled. The residual glass was dissolved in 95% ethanol (total volume, 120 ml).

Part of this ethanol solution (110 ml) was shaken under an atmosphere of hydrogen (35–60 lb/in²) at room temp overnight with 5% palladium–charcoal (3·0 g) and conc HCl (1 drop). After the catalyst and solvent were removed, the residue was recrystallized 3 times from aqueous ethanol. The product melted over a wide range beginning at 56·5° (11·3 g).

This mixture (9·7 g) was heated for 5 hr at 165° with potassium hydroxide (20 g), water (10 ml), and diethylene glycol (200 ml). The resulting solution was diluted with water. The precipitate, which was shown by infrared to be O-methyl-7-methylpodocarpinol, was removed by filtration. Acidification of the filtrate gave a solid which was recrystallized from aqueous methanol (charcoal); 2·27 g; λ_{max} 2·84, 3·66, 3·72, 5·74, and 5·88 μ (see Table 3). (Found: C, 75·63; H, 8·86. $C_{19}H_{28}O_3$ requires: C, 75·46; H, 8·67%).

Rosenmund reduction of the acid chloride.[16] The acid XII (2·00 g) was refluxed for 40 min with thionyl chloride (2 ml; purified). The excess thionyl chloride was distilled. Benzene was added and distilled yielding a crystalline product.

The crude acid chloride was dissolved in xylene (250 ml) and treated at reflux temp. with a slow stream of hydrogen in the presence of palladium over 5% barium sulfate (0·55 g) for 5 hr. Removal of the catalyst and solvent gave a residual glass which was crystallized from ethanol; 0·51 g; m.p. 194–198·5°. Purification by recrystallization from ethanol followed by sublimation gave the pure *anhydride of* O-*methyl-7-methylpodocarpic acid*; λ_{max} 5·55 and 5·75 μ (see Table 3). (Found: C, 77·45; H, 8·84. $C_{38}H_{50}O_5$ requires: C, 77·78; H, 8·59%).

The mother liquor from the recrystallization of the anhydride was concentrated and then diluted with water. The resulting solid was used for the preparation of the semicarbazone by the method

[17] G. L. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *J. Amer. Chem. Soc.* **75**, 422 (1953).

used above. The product, when recrystallized 4 times from aqueous ethanol (charcoal) melted at 205·5–212·5° and was undepressed on admixture with the semicarbazone prepared from the pure aldehyde.

Methyl O-methyl-7-propylpodocarpate. A solution of methyl O-methyl-7-propionylpodocarpate[6a] (40·0 g) in acetic acid (210 ml) was shaken in an atmosphere of hydrogen (10–30 lb/in²) in the presence of conc HCl (1 drop) and 5% palladium–charcoal (4·0 g) for 24 hr at room temp. The resulting mixture was warmed on a steam-bath. The catalyst was removed and the filtrate was diluted at its b.p. with water until the solution was slightly turbid. The desoxy compound crystallized on cooling; 34·0 g; platelets, m.p. 104–105°; $[\alpha]_D$ +125°; λ_{max} 280 (ε 3240) and 287 mμ (ε 3170). (Found: C, 76·95; H, 9·41. $C_{22}H_{32}O_3$ requires: C, 76·70; H, 9·36%).

Methyl O-methyl-7-propyl-9-oxopodocarpate. To a cool (15°) solution of methyl O-methyl-7-propylpodocarpate (10·0 g) in acetic acid (150 ml) was added a slurry of chromic acid (6·31 g) in water (2·5 ml) and acetic acid (10 ml) at such a rate that the temp of the reaction did not exceed 21°. This reaction was allowed to stand at ice-water bath temp for an additional 30 min and was then allowed to stand at room temp overnight. The solution when diluted with water (total volume, 3·5 l.) gave a solid which was collected, washed with water, and then recrystallized twice from aqueous methanol; 7·9 g; m.p. 115·5–118°; $[\alpha]_D$ +86°; λ_{max} 230·5 (ε 17,300) and 277·5 mμ (ε 13,830), (shoulder at 298 mμ);[18] 5·78 and 5·97 μ. (Found: C, 73·46; H, 8·37. $C_{22}H_{30}O_4$ requires: C, 73·71; H, 8·44%).

Anhydride of O-methylpodocarpic acid (XIII). This substance was isolated as a by-product in the preparation of the amide of O-methylpodocarpic acid. O-methylpodocarpic acid (21·2 g) was converted to the crude acid chloride.[6b] This material was stirred into conc ammonium hydroxide (250 ml). The resulting mixture was heated on the steam-bath for 5 min with stirring. The product was taken up in a mixture of benzene and ether. This solution was washed with water, 10% sodium hydroxide, and then with water. The washed solution was stripped to give a residual glass. Treatment of this residue with acetone (400 ml) gave a white granular solid (1·4 g). This solid was recrystallized twice from aqueous acetic acid. The anhydride of O-methylpodocarpic acid crystallized as short needles; λ_{max} 5·59 and 5·76 μ (Table 3). (Found: C, 76·91; H, 8·13. $C_{36}H_{46}O_5$ requires: C, 77·38; H, 8·30%).

Acknowledgement—We are highly indebted to Dr. P. Sengupta of the East India Pharmaceutical Works Ltd., Calcutta-34, India, for the gift of the nimbiol and the nimbiol methyl ether.

[18] Compare with the isomeric methyl O-methyl-7-propionylpodocarpate[6a] m.p. 103.5–105°; $[\alpha]_D$ +134°, $\lambda_{max}^{ethanol}$ 255 (ε 10,500) and 315 mμ (ε 4090).

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THE STRUCTURE OF AROMATIC DIAZO-COMPOUNDS

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IN connexion with the structure[1] of aromatic diazocompounds it is generally accepted that:

1. The diazocompounds in aqueous solution exist as molecules and ions with their equilibrium shifted towards ionization.[2]

2. The diazohydrate is amphoteric[3] and in aqueous solutions is present in negligible amounts.

3. The diazocation and the anion have conjugated bonds.[4]

4. Only the diazocation can take part in coupling reactions.[5] This principle established independently by many authors practically refutes Hantzsch's stereoisomeric theory.

5. The diazohydrate and the nitrosaminic acid (the nitrosamine) are the tautomeric forms,[6] and in diazocompounds there are two acids (the diazohydrate and the nitrosaminic acid) and one base (the diazohydrate). This does not mean the diazocation and -anion which represent the acid and the base according to the Lewis–Ussanovitch theory.[7]

6. The reaction between the diazonium salt and alkali belongs to the class of slow ionic reactions.[8] This, together with the amphoteric nature of the diazohydrate is responsible for the most characteristic properties of diazocompounds.

Schwarzenbach[10] investigating the behaviour of dibasic aprotonic acids, showed that in some cases the second ionization constant is greater than the first. Zollinger[9] applied these considerations to diazocompounds regarding the diazocation as dibasic aprotonic acid possessing similar properties. Accordingly, in the neutralization of the diazonium salt by alkali he assumed that first stage addition of one

[1] See the review in *Usp. Khimi.* XXVIII, No. 9, 1036 (1959).
[2] H. Zollinger, *Chemie der Azofarbstoffe* p. 52. Birhäuser, Basel (1958); C. Wittwer and H. Zollinger, *Helv. Chim. Acta* **37**, 1954 (1954); cf. B. A. Porai-Koshits and J. E. Brüske, *Trudy Leningrad, Tekhnol. Inst. im. Lensoveta* **60**, 92, 111 (1960).
[3] B. A. Porai-Koshits and I. V. Grachev, *Zh. Obshch. Khim.* **16**, 4–5, 571 (1946).
[4] B. A. Porai-Koshits and I. V. Grachev, *Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk* No. 1, 137 (1938); H. Zollinger, *Chemie der Azofarbstoffe* p. 49. Birkhäuser, Basel (1958); cf. K. Holzach *Die Aromatischen Diazoverbindungen.* Stuttgart (1947); E. Müller, *Neuere Anschauungen der Organischen Chemie* 2 Aufl., p. 461. Springer, Berlin (1957).
[5] W. Dilthey and C. Blankenburg, *J. Prakt. Chem.* (2), **142**, 177 (1935); R. Wistar and P. D. Bartlett, *J. Amer. Chem. Soc.* **63**, 413 (1941); R. Hauser and D. S. Breslow, *Ibid.* **63**, 418 (1941); B. A. Porai-Koshits, *Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk* No. 1, 79 (1944); B. A. Porai-Koshits and I. V. Grachev, *Zh. Obshch. Khim.* **16**, 4–5, 571 (1946); C. K. Ingold, *Structure and Mechanism in Organic Chemistry* p. 297. London (1953).
[6] A. Hantzsch, M. Schümann and A. Engler, *Ber. Dtsch. Chem. Ges.* **32**, 1703 (1899); A. Engler, *Ibid*, **33**, 2188 (1900).
[7] G. N. Lewis, *J. Franklin Inst.* **226**, 292 (1938); M. I. Ussanovitch, *Zh. Obshch. Khim.* **9**, 182 (1939).
[8] B. A. Porai-Koshits and B. V. Passet, *Trudy Leningrad, Tekhnol. Inst. im. Lensoveta* **46**, 133 (1958).
[9] H. Zollinger, *Chemie der Azofarbstoffe* p. 53. Birhäuser, Basel (1958).
[10] G. Schwarzenbach, *Helv. Chim. Acta* **26**, 420 (1943).

hydroxyl ion to the diazocation to form the diazohydrate would proceed more slowly that the second stage, the acidic dissociation of the diazohydrate. In this manner he proved theoretically the impossibility of isolating the diazohydrate.

It is believed that the low concentration of the diazohydrate in aqueous solutions does not depend on the properties of the aprotonic acid but results from the amphoteric nature of the diazohydrate. A detailed study of the acid–base equilibrium of the diazocation, the diazohydrate and the diazoanion, the equilibrium being complicated by the tautomeric equilibrium between the diazohydrate and the nitrosaminic acid, reveals that under certain conditions there is complete dissociation of the diazohydrate into ions.[11] These conditions are: (1) the greater magnitude of the product of the acidic and basic constants of the diazohydrate over the magnitude of the ionic product for water.

$$K_a' K_b \gg K_w$$

and, (2) establishing the inequality

$$\frac{K_w^{2'}}{K_w} \gg \frac{K_a}{K_b}$$

where K_a' is the ionization constant of the nitrosaminic acid.

We were able to deduce the formulae for the acidic and basic constants of the diazohydrate.

These formulae are accurate provided the dissociation constant is of the nitrosaminic acid is greater than that for the diazohydrate.

$$K_a = \frac{C \cdot K \cdot [H^+]I}{[H^+]^3_1 - 2C \cdot K} \quad \text{and} \quad K_b = \frac{C \cdot K_w [H^+]I}{[H^+]^3_1 - 2C \cdot K}$$

C is the concentration of the diazonium salt. $[H^+]_1$ is the concentration of the hydrogen ions in the diazonium salt solution, K_w is the water ionic product for water and $K = [H^+]^2$.

In the latter expressions $[H^+]$ is the concentration of the hydrogen ions in the solution obtained by the addition of one equivalent of alkali to the diazonium salt, i.e., the diazonium–diazotate in solution.

It is now possible to substitute the ideas based on the theory of electrolytic dissociation for Schwarzenbach's conception as regards "the unusual properties of aprotic acid".

So far, there is no general agreement as to the stereoisomerism of the aromatic diazocompounds. As far as the stereoisomerism of covalent diazocompounds is concerned, this isomerism does not appear to be proved. Nevertheless, the resemblance of the above compounds to azo compounds whose stereoisomerism is beyond doubt[12] is probable.[13]

Although the isolation of two stereoisomeric forms of covalent diazocompounds proves the presence of stereoisomerism of the compounds involved, but it does not confirm the authenticity of the well known Hantzsch theory. This theory does not

[11] J. E. Brüske and B. A. Porai-Koshits, *Trudy Leningrad, Tekhnol. Inst. im. Lensoveta* **60**, 103 (1960).
[12] G. S.-Hartley, *Nature, Lond.* **140**, 281 (1938); *J. Chem. Soc.* 633 (1938).
[13] R. J. W. Le Fèvre and J. B. Sousa, *J. Chem. Soc.* 3154 (1955); A. Hantzsch, *Ber. Dtsch. Chem. Ges.* **27**, 1894, 3527 (1894); A. Claus, *J. Prakt. Chem.* (2), **50**, 239 (1894).

involve the existence of stereoisomerism in general, but the correlation of the steric structure of diazocompounds and their reactivity.

It has been fully established that the only particle capable of taking part in the diazocoupling reaction is the diazonium cation. The chief argument in favour of the Hantsch theory is the supposed isolation of two stereoisometic salts.[14] Therefore, the supporters of the stereoisomeric hypothesis, linked up the alkaline "syn-salt" with the diazocation. Recently, Zollinger advanced the opinion that in aqueous solutions the equilibrium between the "syn-salt" and the diazocation is established instantly whereas that between the "anti-salt" and the same diazocation takes place slowly and from this the "apparent high reactivity of the syn-salt" results.[15]

Consideration of this statement reveals that it is based on misunderstanding: If the "syn-diazotate" changes into the diazonium cation more readily than the "anti-diazotate", the former possesses not an "apparent" but a really high reactivity.

This hypothesis supports the Hantzsch theory, as it indicates that under all conditions the solution contains the "syn-salt" rather than the diazocation.

The hypothesis of stereoisomerism of diazo alkaline salts not only explains the properties of diazocompounds but accounts for the existence of two different diazo alkaline salts.

So far the isolation of two diazo alkaline salts as two separate substances with the same composition but different properties has not been verified. Similar substances have been synthesized[16] but without any critical approach to the phenomena observed. Some workers consider that structural isomerism[17] may account for the existence of two salts. It was decided to investigate the Hantsch theory concerning the structure of the two alkaline salts and draw attention to the connection between "syn-salts" and the diazonium cation.

In order to determine if the structural isomerism of salts occurs aqueous solutions of *p*-nitrophenyldiazonium salts were titrated potentiometrically by means of the glass electrode with (1) potassium hydroxide and (2) tetra-alkyl-ammonium hydroxide (the triethyl-benzyl-ammonium hydroxide). Both titration curves were identical.[18] As the salts formed from the diazocompound and the tetrasubstituted ammonium base is completely dissociated, this must also be the case for the alkaline salt. Thus the covalent structure of the diazo alkaline salts is impossible. Hence the structural isomerism is impossible since the two acids (the diazohydrate and the nitrosaminic), being tautomeric, can yield but one salt. In spite of these considerations some investigators assume the possibility of the diazotate anions, stereoisomerism arbitrarily fixing the double bond between the nitrogen atoms in the diazotate anion.[19]

The potassium infra-red spectra of some diazocompounds show absorptions at frequencies characteristic of N-nitrosogroup (1385 cm^{-1}) but less pronounced, as well as a very slight absorption at (1574 cm^{-1}) characteristic of the azo group. At the same time N-nitrosomethylaniline and methylazobenzene, studied as standard

[14] A. Hantzsch and D. Gerilowski, *Ber. Dtsch. Chem. Ges.* **28**, 2002 (1895); D. Gerilowski, *Ibid.* **29**, 1075 (1896); A. Hantzsch, *Ibid.* **29**, 743 (1896).
[15] H. Zollinger, *Chemie der Azofarstoffe* p. 61. Birhäuser, Basel (1957).
[16] E. Bamberger and O. Bandisch, *Ber. Dtsch. Chem. Ges.* **45**, 2055 (1912); K. H. Saunders, *The Aromatic Diazocompounds* (2nd Ed.), Chap. XI. London (1949).
[17] A. Hantzsch and G. Reddelien, *Die Diazoverbindungen*. Berlin (1921).
[18] B. A. Porai-Koshits and B. V. Passet, *Trudy Leningrad. Tekhnol Inst. im. Lensoveta* **46**, 134 (1958); *Zh. Obshch. Khim.* **29**, 1407 (1959).
[19] H. Zollinger, *Chemie der Azofarbstoffe* p. 61 *et seq.* Birkhäuser, Basel (1958).

compounds, produced quite distinct absorption bands at the frequencies indicated. This proves that there is a system of conjugated bonds in the diazotate anion resembling rather the nitrosamine than the azo compound structure. Hence, the hypothesis of the stereoisomerism of the diazotate ions should be rejected.

Titrating potentiometrically the *p*-nitrophenyldiazonium salt at different rates, curves obtained by rapid titration characterize the equilibrium not yet established. Only by special procedure were curves representing the stable equilibrium obtained.

Unfortunately, the equilibrium curve for the diazosulphanilic acid was not

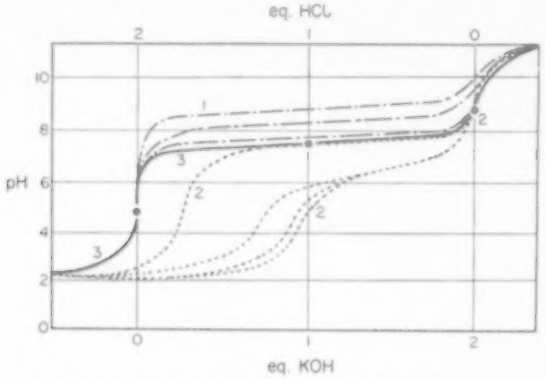

FIG. 1. The alkali and acid titration of *p*-nitrodiazobenzene at 10° at different rates.
1—the curves obtained by direct titration with alkali; the titration rates (from top to bottom); the maximum one practically got: 0·1 equiv/min; 0·04 equiv/min;
2—the curves of back titration with acid; the titration rates (from bottom to top) the maximum one practically obtained; 0·6 eq/min; 0·2 eq/min; 0·005 eq/min;
3–equilibrium curve.

obtained, as in this case, the reaction between the diazonium salt and the alkali proceeds more slowly than in the case of the diazo-*p*-nitroaniline, and the diazocompound decomposes before the equilibrium has been reached.

The study of the electronic spectra of aqueous solutions of diazocompounds from *p*-nitroaniline, sulphanilic acid, chloranilines, aniline and many other amines in acidic and alkaline media of various concentrations show that there are isobastic points for the group of curves representing each diazocompound (see Figs. 2, 3 and 4). These isobastic points prove that in aqueous solutions there are only two substances or particles which are in mobile equilibrium. These particles in acidic and alkaline media appear to be the diazo-cation and the -anion respectively.

The isobastic points for the diazo-*p*-nitroaniline were observed independently by Lewis and Suhr[20]. They measured the absorption spectra of solutions, without providing for the equilibrium which is established and, therefore, they could neither obtain accurate results nor provide an explanation.

In accordance with the results of spectral analysis we developed a method of separate quantitative estimation of diazocation and concentrations in solution for diazo-*p*-nitroaniline[21] and diazosulphanilic acid.[22]

As all this work has been carried out with aqueous (in some cases alkaline) diazosulphanilic acid solutions (e.g. while studying electronic spectra) and other

[20] E. S. Lewis and H. Suhr, *J. Amer. Chem. Soc.* **80**, 1367 (1958).
[21] B. A. Porai-Koshits and B. V. Passet, *Zh. Prike. Khim. iss.* **11**, 2580 (1959).
[22] B. A. Porai-Koshits and Ching Kvrn Tay, *Trudy Leningrad, Tekhnol. Inst. im. Lensoveta* **60** (1960).

compounds but not with the "syn-salt" synthesized by Hantzsch, we considered the investigation of Hantzsch "syn-salt" very important.

Accordingly, the "syn-salt" indentical in all respects with that described by Hantzsch[23] was prepared. Its most important property, viz, the capacity of entering

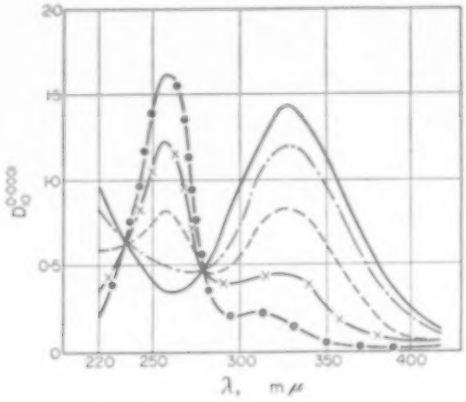

FIG. 2. The *p*-nitrodiazobenzene aqueous solutions absorption curves at various values of pH. ——·——·—— pH = 4·0; —×—×—×— ph = 7·38; — — — — pH = 7·67; ●—●—●—● pH = 7·98; ——— pH = 11·0

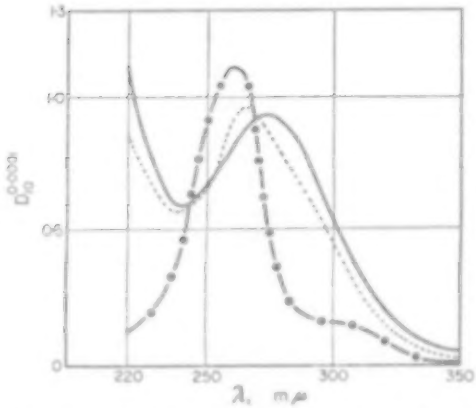

FIG. 3. The diazobenzene aqueous solutions absorption curves at various values of pH. ●—●—●—● pH = 3·0; . . . . . pH = 9·0; ——— pH = 11·0

into the diazocoupling reactions, depends both on the method of preparation and on the length of time of keeping. Thus, having been isolated and rapidly filtered, the preparation possesses the capacity of diazocoupling, the yield of azo dyes being nearly quantitative. Dried to constant weight and prepared for elementary analysis (according to Hantzsch) the "syn-salt" exhibits only 11–15 per cent diazocoupling. After keeping for half a year it completely loses the capacity of diazocoupling.

Hence, according to the period of keeping there are various forms of the "syn-salt" differing from one another in their capacity to enter into the diazocoupling reaction.

[23] A. Hantzsch and D. Gerilowski, *Ber. Dtsch. Chem. Ges.* **28**, 2002 (1895).

Since only the diazocation takes part in the diazocoupling reaction it was concluded that the "syn-salt" prepared for analysis consisted of 11–15% diazonium salt with the required amount of the alkali and the diazo alkaline salt. Comparing the results of our own elementary analyses with those of Hantzsch this conclusion was confirmed.

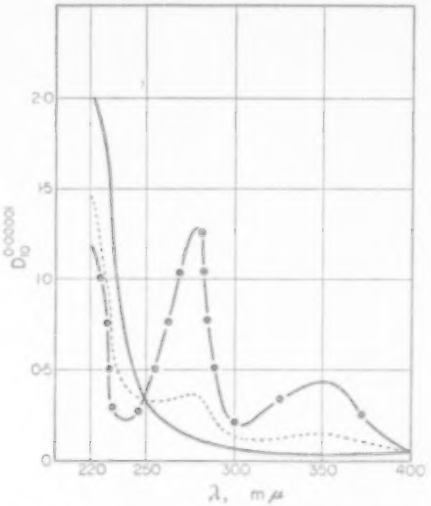

FIG. 4. The 2,6-dichlordiazobenzene aqueous solution absorption curves at various values of —●—●—●— pH = 4·0; ..... pH = 7·7; ——— pH = 11·0

Hantzsch considered the "syn-salt" as homogeneous and in order to accept the analytical data obtained, he supposed that the "syn-salt" crystallized with 1·5 molecules of water.

By means of diazocoupling in buffer solutions with 2-naphtol and the subsequent colorimetry of the solutions obtained, our assumption that the analytical sample of "syn-salt" was a mixture of substances has been confirmed. The sample contained 11·3 per cent of the diazonium salt.

In addition, a sample of this "syn-salt" was titrated with phenyl-methyl-pyrozolone-sulphonic acid following the usual procedure adopted for the determination of diazonium salt,[24] and the results obtained show 11·4 per cent of diazonium salt.

Another sample of the "syn-salt" containing 31 per cent of the diazonium salt (According to phenyl-methyl-pyrozolone-sulphonic acid titration), was titrated potentiometrically and polargraphically and the percentage diazonium salt confirmed. The so-called "anti-salt" (i.e. an ordinary diazo "alkaline salt") showed no oxidizing properties during the titration and the diazocation produced a curve the height of which corresponds to the quantity of the diazocation in the solution. These results are in accordance with Hodgson and Marsden[25] who showed that the "syn-salt" is reduced by sodium-stannite while the "anti-isomer" fails to enter into this reaction.

In order to reject the conception of "instantly set in equilibrium syn-salt-diazocation" we obtained the electronic absorption spectra of the diazonium salt from the

[24] I. V. Grachev, *Factory Lab.* **2**, 154 (1945); *Ibid.* **4–5**, 435 (1946).
[25] H. Hodgson and E. Marsden, *J. Chem. Soc.* 207 (1945).

sulphanilic acid (i.e. in acidic media), the "anti-salt" (in alkaline media), the "syn-salt" (containing 11·3 per cent of diazonium salt) and the diazonium salt mixtures with the "anti-salt" at pH corresponding to the "syn-salt" solution. The "syn-salt" absorption curve coincided with the mixture curve of the diazonium salt and "anti-salt" containing 11·5 per cent of diazonium salt (Fig. 5) and hence, Zollinger's considerations are invalid.

Instead of the "stereoisomeric" hypothesis which has not been confirmed we

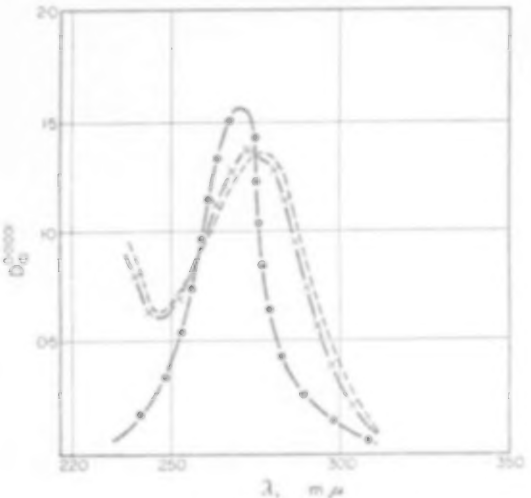

FIG. 5. The *p*-diazobenezenesulphonic acid aqueous solutions absorption curves. —●—●—●— The cation absorption curve (acid medium) ———— the so-called "syn-salt" absorption curve at pH = 10·0. —○—○—○— the points of the curve representing the 11·5% diazonium salt with 88·5% "anti-salt" and alkali mixture. ———— the anion absorption curve (alkali medium).

suggest that the properties of aromatic diazocompounds depend on a state of complex equilibria as follows:*

$$R{-}N{=}N{-}Ac \underset{Ac^-}{\overset{H^+}{\rightleftharpoons}} R{-}N{=}N^+ \underset{H^+}{\overset{OH^-}{\rightleftharpoons}} R{-}N{=}N{-}OH \underset{H^+}{\overset{OH^-}{\rightleftharpoons}} R{-}N_2O \underset{OH^-}{\overset{H^+}{\rightleftharpoons}} R{-}NH{-}NO$$

The position of the first partial equilibrium in this general equation

$$R{-}N{=}N{-}Ac \rightleftharpoons R{-}N_2^+ + Ac^-$$

depends on the strength of the acid HX.[26] The weaker the acid the more this equilibrium is shifted to the left and the equilibrium constant for acetic acid according to De-Tar[27] is less than 10.[5]

Hence by applying weak acids, such undissociated substances as diazoacetate, diazocyanide and diazosulphonate etc can be isolated. Evidently stereoisomers are likely to be found among these covalently built substances.

The application of strong acids shifts this equilibrium to the right; the decrease

* These equilibria have been previously discussed.

[26] A. Hantzsch, *Ber. Dtsch. Chem. Ges.* **33**, 2179 (1900); A. Hantzsch and H. Euler, *Ibid.* **34**, 4166 (1901).
[27] D. F. De-Tar, *J. Amer. Chem. Soc.* **77**, 1745 (1955).

and solubility of the diazonium ionized salts favours the isolation of co-called "active" stable diazocompounds. This has application in industry and the compounds may be isolated as sulphates,[28] salts of aromatic sulphonic acids [29] or in the form of double salts with the salts of tin,[30] zinc[31] or other metals.[32]

On account of the amphoteric nature of the diazohydrate the following partial equilibrium between the diazonium cation and the diazohydrate is inseparable from the equilibrium between the diazohydrate and the diazotate anion and is perhaps the most important conversion of diazocompounds:

$$R{-}N_2^+ \underset{H^+}{\overset{OH^-}{\rightleftharpoons}} R{-}N{=}N{-}OH \underset{H^+}{\overset{OH^-}{\rightleftharpoons}} R{-}N_2O^-$$

In this equilibrium, the reaction between the diazocation and the hydroxyl ion, proceeds more slowly than the subsequent interaction between the diazohydrate and the second hydroxyl ion. Consequently the equilibrium is established slowly and eventually the solutions do not contain any diazohydrate. For some diazocompounds the above equilibrium was studied quantitatively, the spectral method being applied for determining the quantities of the diazonium cation and the diazotate anion. In the case of diazo-*p*-nitraniline this equilibrium constant[21] was found to be $K = 6{\cdot}3.10^{-16}$.

The slowness of the first stage of the equilibrium is responsible for "the existence of two alkaline salts" and the "syn-salt" is therefore a mixture. The diazonium salt and the alkali react even in the solid state producing the alkaline diazocompound salt. All the properties of the "syn-salt" are in agreement with this approach.

The last partial equilibrium:

$$R{-}N_2O^- \underset{OH^-}{\overset{H^+}{\rightleftharpoons}} R{-}NH{-}NO$$

represents the dissociation-molarization of the nitrosaminic acid. It is characteristic of the tautomeric equilibrium between the nitrosaminic acid and the diazohydrate. Increased alkalinity of the medium shifting the equilibrium towards the diazotate anion which may be isolated by decreasing the solubility of the diazocompound alkaline salts. Such preparations[33] are known as "nitrosamines" and "antidiazotates", names we consider as incorrect.

The alkaline salts of the diazocompounds have found application in the dyeing industry as "passive" stable diazocompounds,[33] i.e. substances which cannot undergo the diazocoupling reaction because they do not contain any diazocation. After treatment with acids these alkaline salts are changed into the diazocation and acquire activity.

In some cases by rapid acidification of the diazocompound alkaline solutions, it is possible to isolate the unstable nitrosaminic acids ("free nitrosamines"). Gradually the nitrosaminic acid precipate dissolves, a spontaneous increased pH of the

[28] Brit. Pat. 21227/94 (M L B); Ger. Pat. 85387 (M L B); *Frdl.* **4**, 673s (1899) Ger. Pat. 622306 (L-G); *Chem. Abstr.* **30**, 5803[1] (1936).
[29] Ger. Pat. 81039; *Frdl.* **4**, 673 (1899).
[30] P. Griess, *Ber. Dtsch. Chem. Ges.* **18**, 965 (1885).
[31] Ger. Pat. 484894 (I-G); *Frdl.* **15**, 569 (1928).
[32] A. N. Nesmejanov, *Ber. Dtsch. Chem. Ges.* **62**, 1018 (1929); *Ibid.* **68**, 1877m (1935).
[33] C. Schraube and C. Schmidt, *Ber. Dtsch. Chem. Ges.* **27**, 514 (1894).

medium taking place. This confirms the idea that the equilibrium between the alkaline salts of the diazocompounds and the mineral acids as well as between the diazonium salt and the alkalis takes place slowly as established by potentiometric titrations.[21]

All the puzzling chemistry of diazocompounds is understood if we take into consideration the amphoteric nature of the diazohydrate, the tautomerism between the diazohydrate and the nitrosaminic acid and, finally, the slowness of some neutralization ionic reactions[34] in particular the reaction between the diazonium cation and the hydroxyl ion.

The only conception of former views which should be retained is the stereoisomerism of the covalently built diazocompounds (such as the diazocyanides, the diazoacetates, etc). But this is beyond the scope of the Hantsch theory and concerns phenomena frequently met in organic chemistry.

[21] O. F. Ginsburg, *Zh. Obshch. Khim.* **23**, 1504, 1677 (1953); A. A. Frost and R. G. Pearson, *Kinetics and Mechanism* p. 113. McGraw-Hill, New York (1953).

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PEPTIDES—XI*

SYNTHESIS OF PEPTIDES DERIVED FROM ALPHA-METHYLALANINE

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Abstract—Union of α-methylalanyl residues in a peptide chain is severely sterically hindered. This hindrance can be overcome by employing either the mixed anhydride (I) of pivalic acid and benzyloxycarbonyl-α-methylalanine or, more generally, oxazolones (II), including 4,4-dimethyl-2-trifluoromethyloxazolone (II; R = CF_3). 4,4-Dimethyloxazolone (II; R = H) has been obtained in solution and characterized by its infra-red spectrum; it is attacked by α-methylalanine methyl ester at the methine group, in contrast to the normal reaction with cyclohexylamine at the carbonyl group.

INCORPORATION of α-methylalanine (α-aminoisobutyric acid) in synthetic peptides has received little attention because this amino acid has not been generally regarded as a constituent of proteins, although this possibility was mooted when 5,5-dimethylhydantoin was reported as a pyrolytic fragment of common proteins.[1] Our discovery of α-methylalanine as a component of an antibiotic[2] prompted us to examine the problem with the eventual aim of synthesizing both cyclic oligopeptides and open-chain peptides, built entirely or partly from α-amino acids lacking a hydrogen atom at the α-position. Not unexpectedly, we encountered difficulties arising from steric hindrance,‡ but on the other hand the problem of preserving optical activity was absent and practical methods for the synthesis of open-chain oligopeptides of this class can now be described.

Abderhalden *et al.*[4,5] prepared peptides of α-methylalanine by Fischer's method, but comparison with the material prepared by us from the benzyloxycarbonyl derivative shows that even the simple dipeptide, α-methylalanyl-α-methyl-alanine, was impure. Bergmann *et al.*[6] synthesized dipeptides of glycine or alanine and α-methylalanine by the carbobenzoxy(benzyloxycarbonyl) method. Although they prepared the benzyloxycarbonyl derivative of α-methylalanine via the ethyl ester, it is available directly, in excellent yield, from the amino acid (see Experimental)§ and it crystallizes well. On the other hand the acid chloride, which they used, without

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‡ The extraordinary slowness[3] of the "polymerization" of N-carboxy-α-methylalanine anhydride is a noteworthy example of this effect.

§ Yields from some other acylations of α-methylalanine have been reported[7] to be low or negligible, presumably as a result of steric hindrance.

[1] T. Yabuta, Z. Saito, K. Takeda and K. Tamari, *Chem. Zentr.* **1**, 221 (1940).
[2] G. W. Kenner and R. C. Sheppard, *Nature, Lond.* **181**, 48 (1958).
[3] H. Weingarten, *J. Amer. Chem. Soc.* **80**, 352 (1958).
[4, 6] E. Abderhalden and F. Gebelein, *Z. physiol. Chem.* **152**, 125 (1926); [5] E. Abderhalden and E. Rossner, *Ibid.* **163**, 149 (1927).
[5] E. Abderhalden and W. Zeisset, *Fermentforschung* **13**, 310 (1932).
[6] M. Bergmann, L. Zervas, J. S. Fruton, F. Schneider and H. Schleich, *J. Biol. Chem.* **109**, 325 (1935).
[7] e.g. W. E. Hanby, S. G. Waley and J. Watson, *J. Chem. Soc.* 3009 (1950); A. Kjaer, *Acta Chem. Scand.* **6**, 327 (1952).

isolation, for reaction with glycine benzyl ester to obtain small amounts of the dipeptide, has eluded us; even under very mild conditions the N-carboxyanhydride is formed by elimination of benzyl chloride. The similar cyclization of benzyloxycarbonylalanine occurs more easily than with the glycine derivative,[8] and evidently a second α-methyl group facilitates it still more.

A serviceable route to dipeptide derivatives in this series is through the chlorides of the tosylamino acids. Thus a 71 per cent yield was obtained from the coupling, in aqueous acetone buffered with magnesium oxide, of glycine with tosyl-α-methylalanyl chloride, and this was superior to the coupling of the acid with glycine ester by the carbodi-imide or mixed anhydride procedures. In contrast, the aqueous coupling of tosylglycyl chloride with α-methylalanine failed, but the methyl ester of the tosyldipeptide was prepared in 71 per cent yield from the chloride and the amino acid ester under anhydrous conditions. The difference between these two aqueous couplings recalls the kinetic data on the formation of amides from esters; the reaction of methyl trimethylacetate with ammonia is approximately 100 times slower than that of methyl propionate,[9] while the reaction between methyl acetate and t-butylamine is immeasurably slow.[10] As a general rule steric hindrance of the usual peptide-forming reactions at the amino group can be expected to be more severe than hindrance of reactions at the carbonyl group in derivatives of α-methylalanine. The aqueous coupling of tosyl-α-methylalanyl chloride with α-methylalanine also failed; in this instance toluene-*p*-sulphonamide was a major product. Evidently the coupling was so slow that it was supplanted by alkaline degradation (Reaction 1) of the acid chloride.[11]

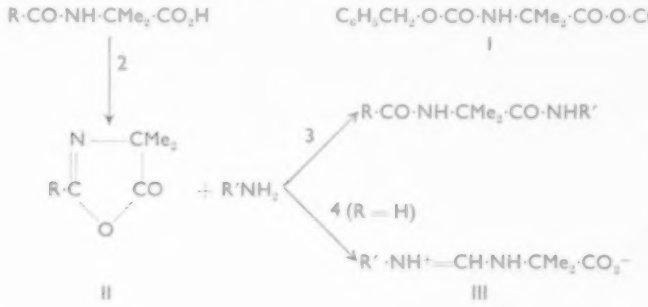
$$Tos{\cdot}NH{\cdot}CMe_2{\cdot}CO.Cl + OH^- \xrightarrow{1} Tos{\cdot}NH_2 + Me_2CO + CO + Cl^-$$

Even when this reaction was prevented by N-methylation, the yield of N-methylated dipeptide derivative was very poor and the main reaction was hydrolysis. However, the methyl ester of tosyl-α-methylalanyl-α-methylalanine was obtained satisfactorily by coupling the acid chloride with the amino acid ester in dry acetone.

Most of the other conventional methods of peptide synthesis are of negligible value for the joining of α-methylalanyl residues. For example, dicyclohexyl carbodi-imide failed to condense formyl-α-methylalanine with α-methylalanine methyl ester. Likewise, there was negligible diminution in the infra-red absorption of the isocyanate derived from this ester when it was heated with benzyloxycarbonyl-α-methylalanine, although it has been reported to combine normally, albeit comparatively slowly, with benzyloxycarbonylglycine.[12] Again, the cyanomethyl ester of benzyloxycarbonyl-α-methylalanine was recovered completely after a prolonged period of attempted reaction with α-methylalanine methyl ester, and the mixed carbonic anhydride method also failed; the yield of dipeptide derivative from the sulphuric anhydride method was only 8 per cent. Our assumption that steric hindrance was responsible for these failures prompted the trial of the mixed pivalic anhydride (I), in which the steric effect would be counter-balanced. Pivaloyl chloride was included in an early survey[13] of

[8] M. Hunt and V. Du Vigneaud, *J. Biol. Chem.* **124,** 699 (1938).
[9] M. Gordon, J. G. Miller and A. R. Day, *J. Amer. Chem. Soc* **70,** 1946 (1948).
[10] E. M. Arnett, J. G. Miller and A. R. Day, *J. Amer. Chem. Soc.*, **72,** 5635 (1950).
[11] [a] R. H. Wiley and R. P. Davis, *J. Amer. Chem. Soc.* **76,** 3496 (1954); [b] A. F. Beecham, *Ibid.* **79,** 3257 (1957).
[12] S. Goldschmidt and M. Wick, *Liebigs Ann.* **575,** 217 (1952).
[13] J. R. Vaughan and R. L. Osato, *J. Amer. Chem. Soc.* **73,** 5553 (1951).

reagents for the mixed carboxylic anhydride method of peptide synthesis, but it appeared slightly inferior to isovaleryl chloride. Recently, however, pivaloyl chloride has proved valuable for the condensation of tosyl-α-amino acids and in the asparagine series.[14] With the triethylammonium salt of benzyloxycarbonyl-α-methylalanine it yielded the crystalline and relatively stable mixed anhydride (I) quantitatively. In turn, reaction between the anhydride (I) and α-methylalanine methyl ester in toluene solution afforded the benzyloxycarbonyldipeptide ester in excellent yield.* With the triethylammonium salt of benzyloxycarbonyl-α-methylalanyl-α-methylalanine, however, pivaloyl chloride yielded (Reaction 2) the oxazolone (II; $R = C_6H_5CH_2{\cdot}O{\cdot}CO{\cdot}NHCMe_2$) rather than a mixed anhydride, and ethyl chloroformate behaved similarly. This oxazolone was more conveniently obtained by dehydration of the benzyloxycarbonyldipeptide with acetic anhydride (see below).



While the absence of a hydrogen atom from the alpha position in α-methylalanine diminishes the value of the customary methods of peptide synthesis, it favours the oxazolone method because there can be neither racemization nor acylation at the alpha carbon atom. Consequently the oxazolones (II) derived from α-methylalanine are, in general, easily manipulated, and they give exceptionally high yields in addition reactions (3) with amines. Indeed the early literature contains examples of the preparation of acetyl and benzoyl peptides containing a residue of α-methylalanine by the oxazolone method.[15] 4,4-Dimethyl-2-trifluoromethyloxazolone (II; $R = CF_3$), prepared (Reaction 2) by a modification of the general method of Weygand and Glöckler[16], is an excellent reagent for the addition of a single α-methylalanyl residue to an amine. Together, this coupling and removal of the trifluoroacetyl group by methanolic hydrogen chloride provide a repetitive method for lengthening the peptide chain of methyl esters. However, alkaline hydrolysis of the trifluoroacetylamino group, and simultaneously the ester group, is more efficient. Thus trifluoroacetyl-α-methylalanyl-α-methylalanine methyl ester was converted, by direct carbobenzoxylation of the alkaline hydrolysate, almost quantitatively into the benzyloxycarbonyl dipeptide. In turn this was dehydrated, as mentioned above, to the crystalline oxazolone, which also reacted cleanly with α-methylalanine methyl ester. Similarly

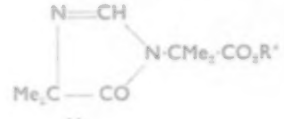
* With the more polar dimethylformamide as solvent, the yield was lower and some pivaloyl-α-methylalanine methyl ester was also formed.

[14] M. Zaoral, *Angew. Chem.* **71**, 743 (1959).
[15] E. Mohr, *J. Prakt. Chem.* **81**, 49, 473 (1910); C. Gränacher and M. Mahler, *Helv. Chim. Acta* **10**, 246 (1927); R. E. Steiger, *Ibid.* **17**, 563 (1934).
[16] F. Weygand and U. Glöckler, *Chem. Ber.* **89**, 653 (1956).

the tosyl derivatives of the di-, tri-, and tetra-peptides of α-methylalanine all gave crystalline, well behaved oxazolones; the tosyl dipeptide was lengthened at the carboxyl end up to the tosyl pentapeptide in 50 per cent overall yield. The oxazolone from tosyl-α-methylalanyl-glycine was obtained in only 60 per cent yield, probably owing to side reactions of the methylene group, but it reacted satisfactorily with α-methylalanine methyl ester in boiling acetone in one hour, conditions too mild for the derivative of α-methylalanyl-α-methylalanine. For this and its homologues acetonitrile was the preferred solvent, and it was better to employ, as the other reagent, the free ester, than its hydrochloride and triethlyamine.

As the formyl protecting group can be removed easily with methanolic hydrogen chloride, we were attracted by 4,4-dimethyl-oxazolone (II; R = H). We have not yet isolated this rather unstable compound, but it is well characterized by the infra-red spectrum of the carbon tetrachloride solution after reaction between formyl-α-methyl-alanine and thionyl chloride in the presence of triethylamine.* (Reaction between this acid and acetic anhydride gave an N-acetylated mixed anhydride (IV) instead of the oxazolone). The solution of 4,4-dimethyloxazolone gave the expected reaction 3 with cyclohexylamine and with glycine ester, although the yield was only 47 per cent in the latter instance. With α-methylalanine methyl ester almost the entire reaction took Path 4, which has an analogy in part of the penillic acid change.[18] Just as aldehydes are more reactive than ketones, so 4,4-dimethyloxazolone should be the oxazolone (II) most prone to reaction 4 and evidently the competition between 3 and 4 in this case is mainly determined by steric hindrance of the normal Reaction 3. Presumably some of the reaction with glycine ester goes along Path 4.

IV



V

VI

The structure (III; $R' = CMe_2 \cdot CO_2Me$) of the abnormal product from 4,4-dimethyloxazolone and α-methylalanine methyl ester is secured by the following evidence. It formed a hydrochloride which was a relatively strong acid (p*Ka* 2·84), comparable to α-amino acid hydrochlorides. On being heated, the amidine (III; $R' = CMe_2 \cdot CO_2Me$) cyclized with loss of methanol yielding the imidazolone carboxylic acid (V; R″ = H); a minor product was the corresponding methyl ester (V; R″ = Me) formed by the alternative cyclization with loss of water. This imidazolone methyl ester was obtained directly by reaction between α-methylalanine methyl ester and ethyl orthoformate. In addition to confirming the structure assigned to the imidazolones (V), this reaction shows that the abnormal product (III) results from attack by the amine at the methine group (Position 2) in 4,4-dimethyloxazolone.

Attempts to obtain the free amidine dimethyl ester corresponding to the

* Unsuccessful attempts to prepare unsubstituted oxazolone hydrochloride have been mentioned.[17] Infra-red spectroscopy has not detected free oxazolone as being produced from formylglycine under our conditions, i.e. in the presence of triethylamine.

[17] F. E. King, J. W. Clark-Lewis, D. A. A. Kidd and G. R. Smith, *J. Chem. Soc.* 1039 (1954).

[18] R. B. Woodward, *Chemistry of Penicillin* (Edited by H. T. Clarke, J. R. Johnson and Sir Robert Robinson) p. 445. University Press, Princeton (1949).

zwitterion (III; R = $CMe_2 \cdot CO_2Me$) were unsuccessful. Thus α-methylalanine methyl ester was converted by formimidoisopropyl ether to the imido ether (VI),[19] but this with α-methylalanine methyl ester again yielded the imidazolone (V; R″ = Me). The imidazolone was also formed by reaction between α-methylalanine methyl ester and dichloromethyl methyl ether, and also when the hydrochloride of (III; R = $CMe_2 \cdot CO_2Me$) was treated with 2 equivalents of diazomethane. Evidently the amidine dimethyl ester cyclizes too rapidly to be isolated. With cyclohexylamine, the imido ether (VI) yielded the N-cyclohexylimidazolone, also formed by thermal dehydration of formyl-α-methylalanine cyclohexylamide in the presence of acid.

The infra-red spectra[20] of the amidine (III; R = $CMe_2 \cdot CO_2Me$), N,N′-diphenyl and N,N′-dicyclohexylformamidines and their hydrochlorides are recorded in the Experimental section, since these show anomalies doubtless due to strong molecular association.

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EXPERIMENTAL

Melting points are uncorrected. Infra-red spectra are of Nujol mulls determined with a Perkin–Elmer Model 21 Spectrophotometer (NaCl optics) unless otherwise stated. Evaporations are under reduced pressure. Neutral products were isolated by washing in ethyl acetate solution successively with dilute hydrochloric acid, sodium hydrogen carbonate solution, and water.

General method for the preparation of oxazolones. A solution of the acylamino acid or peptide (5 mmoles) in acetic anhydride (20 cc) was heated at 110–120° (oil bath) for 15 min and then evaporated. Last traces of acetic anhydride were removed by addition of toluene (20 cc) and evaporation, and the residual oxazolone recrystallized.

α-Methylalanine methyl ester. The methyl ester hydrochloride was prepared from α-methylalanine[21] by the usual Fischer method. The methyl ester (70% yield from the amino acid), b.p. 130–138°, was liberated by ammonia in chloroform solution.[22]

α-Methylalanyl-α-methylalanine. The *hydrobromide*, m.p. 213–215° (Found: C, 35·5; H, 6·6; N, 10·2. $C_8H_{15}O_3N_2Br$ requires: C, 35·7; H, 6·4; N, 10·4%) was obtained from the benzyloxycarbonyl derivative (see below) by the action of hydrogen bromide in acetic acid. Passage of an aqueous solution of the hydrobromide through a column of Dowex-1 × 4 anion-exchange resin (acetate form) afforded the free *dipeptide*, no m.p. below 300°, ν_{max} 3378, 3077, 2564, 2151, 1684, 1653, 1634, 1610, 1575, 1493, 1351, 1300, 1290, 1241, 1209, 1168, 1094, 1003, 955, 939, 918, 880, 798, 794, 769 cm^{-1} (Found: C, 51·2; H, 8·75; N, 14·7. $C_8H_{16}O_3N_2$ requires: C, 51·05; H, 8·6; N, 14·9%). Abderhalden and Gebelein[23] give m.p. 244–246°.

Trifluoroacetyl Derivatives

Trifluoroacetyl-α-methylalanine

Trifluoroacetic anhydride (4·41 g, slight excess) was added gradually to an ice-cooled solution of α-methylalanine (2·06 g, dried at 100°) in trifluoroacetic acid (8·5 g, distilled from a little phosphoric oxide). After standing overnight at room temp. the solution was evaporated and the crystalline residue extracted with ether. Dilution of the ether with light petroleum and partial evaporation afforded needles of *trifluoroacetyl-α-methylalanine* (3·61 g, 90%), m.p. 167–171·5°. The analytical sample, m.p. 170·5–172°, was sublimed at 140°/14 mm (Found: C, 36·2; H, 4·2; N, 7·3. $C_6H_8O_3NF_3$ requires: C, 36·2; H, 4·1; N, 7·0%).

4,4-Dimethyl-2-trifluoromethyloxazolone (II; R = CF_3)

Throughout the preparation, atmospheric moisture was excluded by drying tubes containing phosphoric oxide. Trifluoroacetyl-α-methylalanine (5·20 g, dried at 80°) was dissolved in thionyl chloride (6 cc) at 50–70°, with vigorous evolution of hydrogen chloride. The excess thionyl chloride

[19] cf. J. W. Cornforth and R. H. Cornforth, *J. Chem. Soc.* 96 (1947).
[20] cf. J. Fabian, M. Legrand, and P. Poirier, *Bull. Soc. Chim. Fr.* 1499 (1956).
[21] H. T. Clarke and H. J. Bean, *Org. Syntheses* Coll. Vol. II, 29 (1943).
[22] G. Hillman, *Z. Naturf.* **1**, 682 (1946).

was evaporated at room temp and quinoline (3·87 g, slight excess) added to the residue. The mixture was heated for a few min at 80–120° (oil bath) and then distilled, yielding 4,4-*dimethyl-2-trifluoromethyloxazolone* (3·76–4·27 g, 80–91%), b.p. 112–116°, ν_{max} (film) 3003, 2950, 1835, 1689, 1462, 1439, 1385, 1366 cm^{-1} (Found: C, 40·2; H, 3·3; N, 7·5. $C_6H_6O_2NF_3$ requires: C, 39·8; H, 3·3; N 7·7%). The compound is rapidly hydrolysed by atmospheric moisture but otherwise stable. In the absence of quinoline the acid chloride, unlike those of other trifluoroacetylamino acids,[16] sublimes unchanged.

Trifluoroacetyl-α-methylalanyl-α-methylalanine methyl ester

α-Methylalanine methyl ester (1·17 g, slight excess) was added gradually to an ice-cold solution of 4,4-dimethyl-2-trifluoromethyloxazolone (1·27 g) in dry acetonitrile (5 cc). The mixture was kept for 10 min before being heated (steam bath) for 10 min and evaporated. Recrystallization of the residue from benzene afforded the *dipeptide derivative* (2·06 g, 98%), m.p. 111·5–115° raised to 113·5–115·5° by a second recrystallization (Found: C, 44·4; H, 5·6; N, 9·3. $C_{11}H_{17}O_4N_2F_3$ requires: C, 44·3; H, 5·7; N, 9·4%).

Trifluoroacetyl-α-methylalanyl-α-methylalanyl-α-methylalanine methyl ester

Hydrogen chloride was bubbled through a boiling solution of the foregoing dipeptide derivative (1·5 g, 5 mmoles) in dry methanol (100 cc) during 2½ hr. After evaporation, the hygroscopic residue (1·15 g), was dissolved in dry acetonitrile (20 cc), triethylamine (0·51 g, 5 mmoles) added and the solution filtered. 4,4-Dimethyl-2-trifluoromethyloxazolone (0·906 g, 5 mmoles) was added to the ice-cooled filtrate, which was kept for 10 min before being heated (steam bath) for 10 min. The acetonitrile was evaporated and the neutral fraction isolated. When the dried (Na_2SO_4) ethyl acetate solution was concentrated and cooled it furnished the *tripeptide derivative* (1·14 g, 60%), m.p. 197–199° (Found in material sublimed at 150–175°/0·1 mm: C, 47·1; H, 6·2; N, 11·0. $C_{14}H_{24}O_5N_3F_3$ requires: C, 47·0; H, 6·3; N, 11·0%).

Benzyloxycarbonyl Derivatives

Benzyloxycarbonyl-α-methylalanine

To an ice-cold solution of α-methylalanine (5·02 g) in 1·67 N NaOH (30 cc) and acetone (25 cc), adjusted to pH 10·9, was gradually added benzyl chloroformate (16 g of 80% pure) in dry acetone (25 cc) during 70 min with stirring. The pH of the solution was maintained at 10·8–10·9 by simultaneous addition of 2 N NaOH (37 cc). The mixture was stirred during 2 hr at room temp before being concentrated and acidified. The precipitated oil was extracted into ethyl acetate and the acidic fraction isolated with sodium carbonate solution in the usual manner. The oily product crystallized slowly, and was recrystallized from ether–light petroleum (10·9 g, 92%), m.p. 67–70° raised to 72·5–74·5° by one further recrystallization from benzene–light petroleum (Found: C, 60·7; H, 6·6; N, 5·95. Calc. for $C_{12}H_{15}O_4N$: C, 60·75; H, 6·4; N, 5·9%). Bergmann *et al.*[6] report m.p. 78°.

Benzyloxycarbonyl-α-methylalanine cyanomethyl ester

A mixture of benzyloxycarbonyl-α-methylalanine (5·93 g), triethylamine (5·28 cc), and chloroacetonitrile (7·55 g) was kept at 70–75° during 40 min. After the excess chloroacetonitrile had been evaporated the neutral product (6·33 g, 90%), m.p. 42–47°, was isolated with ethyl acetate in the usual manner. Recrystallization from ether at −10° furnished the pure *cyanomethyl ester*, m.p. 45–48·5° (Found: C, 61·1; H, 5·5; N, 10·05. $C_{14}H_{16}O_4N_2$ requires: C, 60·9; H, 5·8; N, 10·1%). This ester (2·76 g) was recovered in 97% yield after being heated during 4 hr with a boiling mixture of ethyl acetate (3 cc), α-methylalanine methyl ester (2·34 g), and acetic acid (0·030 g) either with or without triethylamine (5 cc).

Benzyloxycarbonyl-α-methylalanine cyclohexylamide

The general route[23] via the lithium salt of benzyloxycarbonyl-α-methylalanine and the sulphuric anhydride gave an 83% yield of the crude neutral product. Recrystallization from benzene–light petroleum furnished the pure *cyclohexylamide* (76%), m.p. 124–127° (Found: C, 68·1; H, 7·95; N, 8·8. $C_{18}H_{26}O_3N_2$ requires: C, 67·9; H, 8·2; N, 8·8%).

[23] D. W. Clayton, J. A. Farrington, G. W. Kenner and J. M. Turner, *J. Chem. Soc.* 1398 (1957).

Benzyloxycarbonyl-α-methylalanine pivalic acid mixed anhydride (I)

Pivaloyl chloride (3·6 g, 30 mmole) was added to a stirred and cooled (−5°) solution of benzyloxycarbonyl-α-methylalanine (7·11 g, 30 mmoles) and triethylamine (3·03 g, 30 mmoles) in dry toluene (15 cc). After 2 hr at −5° and 1 hr at room temp, the solution was filtered and the filtrate evaporated to yield the *mixed anhydride* (9·52 g, 99%), m.p. 82–86°. The analytical sample had m.p. 81–83° after recrystallization from toluene–light petroleum, ν_{max} 3290, 1805, 1736, 1678 and 1531 cm^{-1} (Found: C, 63·6; H, 7·3; N, 4·6. $C_{17}H_{23}NO_5$ requires: C, 63·5; H, 7·2; N, 4·3%).

Benzyloxycarbonyl-α-methylalanyl-α-methylalanine methyl ester

The foregoing mixed anhydride (6·42 g, 20 mmoles) was added to dry toluene (100 cc) containing α-methylalanine methyl ester (2·67 g, 22 mmoles) and the solution heated at 60° for 3 hr. After standing overnight at room temp, the reaction mixture was diluted with ethyl acetate and the neutral product isolated in the usual manner. Recrystallization from ether–light petroleum afforded the *dipeptide derivative* (5·9 g, 89%), m.p. 107–109°. A sample recrystallized once further had m.p. 109–111° (Found: C, 60·7; H, 7·2; N, 7·9. $C_{17}H_{24}O_5N_2$ requires: C, 60·7; H, 7·2; N, 8·3%). When the toluene was replaced by dimethylformamide as solvent, the crude neutral product contained pivaloyl-α-methylalanine methyl ester (20–30%, I.R. spectrum), and the isolated yield of pure dipeptide derivative was lower (57%).

Pivaloyl-α-methylalanine methyl ester

This *compound*, prepared from α-methylalanine methyl ester hydrochloride (1·53 g, 10 mmoles), triethylamine (2·02 g, 20 mmoles), and pivaloyl chloride (1·20 g, 10 mmoles) in toluene (20 cc) kept overnight at room temp, had m.p. 92–93° after two crystallizations from ether (Found: C, 60·1; H, 9·7; N, 6·7. $C_{10}H_{19}NO_3$ requires: C, 59·7; H, 9·5; N, 7·0%).

Benzyloxycarbonyl-α-methylalanyl-α-methylalanine

(a) A mixture of trifluoroacetyl-α-methylalanyl-α-methylalanine methyl ester (2·98 g) and N NaOH (30 cc) was kept overnight at room temp. Trifluoroacetic acid was added to pH 6 and the crystalline residue from evaporation dissolved in water (20 cc) and acetone (15 cc) and brought to pH 10·9 by addition of N NaOH. Benzyl chloroformate (3·20 g of 80%) in acetone (20 cc) was added during 35 min to the cooled and stirred solution of dipeptide, the pH being maintained at 10·7–11 by further addition of alkali. Stirring was continued at room temp for 1 hr, and then the usual extraction procedure furnished the *benzyloxycarbonyl dipeptide* (3·05 g, 94%), m.p. 157–159° raised by recrystallization from aqueous methanol to 161–162·5° (Found: C, 59·7; H, 6·6; N, 8·9. $C_{16}H_{22}O_5N_2$ requires: C, 59·6; H, 6·9; N, 8·7%). Diazomethane in ethereal solution converted this acid into the foregoing methyl ester, m.p. and mixed m.p. 111°.

(b) A solution of benzyloxycarbonyl-α-methylalanyl-α-methylalanine methyl ester (0·336 g, 1 mmole) in dioxan (5 ml) containing 2 N HCl (1 cc) was heated under reflux for 6 hr and then left overnight at room temp. After evaporation of the dioxan, the acidic product was isolated with ethyl acetate and sodium carbonate solution in the usual way. Evaporation yielded the benzyloxycarbonyl dipeptide (0·233 g, 72·5%), m.p. 140–154°, raised by one recrystallization from aqueous methanol to 157–160°.

2-(1′-*Benzyloxycarbonylamino-1′-methyl)ethyl-4,4-dimethyloxazolone*

(II; R = $C_6H_5CH_2$·O·CO·NH·CMe_2)

(a) This *oxazolone* was prepared from benzyloxycarbonyl-α-methylalanyl-α-methylalanine (1·23 g) by the general procedure already described. Yield 1·19 g (98%), m.p. 125–126·5° (Found: C, 63·3; H, 6·7; N, 9·2. $C_{16}H_{20}O_4N_2$ requires: C, 63·1; H, 6·6; N, 9·2%).

(b) Ethyl chloroformate (0·11 cc, 1 mmole) was added to a solution at −5° of benzyloxycarbonyl-α-methylalanyl-α-methylalanine (0·322 g, 1 mmole) and triethylamine (0·14 cc, 1 mmole) in dry toluene (10 cc). The mixture was kept at −5° for 2 hr and at room temp for 1 hr before being filtered and evaporated at low temp. There was obtained 0·320 g (103%) of crude oxazolone, m.p. 120–123°, identical in I.R. spectrum with the above product.

(c) Dehydration of the dipeptide derivative (1 mmole) with pivaloyl chloride (1·5 mmole) and triethylamine (1·5 mmoles) under the same conditions as in the preceding experiment likewise

afforded the crude oxazolone (98%), m.p. 122–123° after recrystallization from ethyl acetate–light petroleum (yield 80%).

Benzyloxycarbonyl-α-methylalanyl-α-methylalanyl-α-methylalanine methyl ester

A solution of the foregoing oxazolone (0·364 g) and α-methylalanine methyl ester (0·35 g) in acetonitrile (8 cc) was kept at 100° during 6 hr and then evaporated. Recrystallization of the residue from aqueous methanol afforded the *tripeptide derivative* (0·461 g, 91%), m.p. 145–146° (Found: C, 59·8; H, 7·2; N, 10·25. $C_{21}H_{31}O_6N_3$ requires: C, 59·8; H, 7·4; N, 10·0%).

Tosyl Derivatives

Tosylglycyl-α-methylalanine methyl ester

A solution of tosylglycyl chloride (2·48 g, 10 mmoles) in dry acetone (20 cc) was added in 4 portions to a cooled, shaken solution of α-methylalanine methyl ester (2·46 g, 21 mmoles) in acetone (25 cc). The mixture was cooled for 30 min further and then left for 1 hr at room temp. The precipitated α-methylalanine methyl ester hydrochloride (1·02 g) was collected before the acetone was evaporated. Concentration of the solution of the neutral product in ethyl acetate yielded the *dipeptide derivative* (2·33 g, 71%), m.p. 113–116°. The analytical sample was recrystallized from aqueous methanol, m.p. 113·5–115° (Found: C, 51·4; H, 6·4; N, 8·5. $C_{14}H_{20}O_5N_2S$ requires: C, 51·2; H, 6·1; N, 8·5%). A similar preparation (threefold scale), in which a mixture of α-methylalanine methyl ester hydrochloride (5·06 g, 33 mmole), triethylamine (6·6 g, 66 mmoles) and dimethylformamide (30 cc) was substituted for the solution of ester (63 mmoles) in acetone, yielded only 47% of the dipeptide derivative.

Tosylglycyl-α-methylalanine

A solution of the foregoing methyl ester (6·23 g, 19 mmoles) in 2 N NaOH (20 cc) was shaken at room temp during 4 hr and then acidified. Recrystallization from aqueous methanol afforded *tosylglycyl-α-methylalanine* (5·80 g, 97%), m.p. 177–178·5° (Found: C, 49·6; H, 5·7; N, 8·9. $C_{13}H_{18}O_5N_2S$ requires: C, 49·7; H, 5·8; N, 8·9%).

Tosyl-α-methylalanine

The following procedure is preferable to published methods. A solution of tosyl chloride (41·8 g, 0·22 mole) in dry acetone (100 cc) and simultaneously 2 N NaOH (110 cc) were added dropwise during 1 hr to a vigorously stirred and cooled solution of α-methylalanine (20 g, 0·2 mole) in 2·5 N NaOH (80 cc) and acetone (80 cc). Stirring was continued for 20 min and then the solution was allowed to reach room temp and left for 1 hr. Acidification after partial evaporation yielded material (35·5 g, 69%) sufficiently pure for further work, m.p. 142–145° raised by recrystallization from aqueous methanol to 151–152° (Found: C, 51·3; H, 6·1; N, 5·2. Calc. for $C_{11}H_{15}O_4NS$: C, 51·4; H, 5·9; N, 5·45%). Previously reported m.p.s are 147°,[24] 143°,[25] 149–150°.[110]

Tosyl-α-methylalanyl chloride

To avoid darkening of the solution, the reaction between tosyl-α-methylalanine and thionyl chloride was carried out at 10–18° during 3 hr and it yielded 73% of material sufficiently pure for further work, m.p. 116–117° (dec) raised by recrystallization from benzene to 120–121° (Found: C, 48·2; H, 5·4; N, 5·0; Cl, 12·9. Calc. for $C_{11}H_{14}O_3NSCl$: C, 47·9; H, 5·1; N, 5·1; Cl, 12·9%). Previously m.p. has been reported[110] as 115–116°.

Tosyl-α-methylalanylglycine

A solution of tosyl-α-methylalanyl chloride (2·10 g, 75 mmoles) in dry acetone (8 cc) was added gradually during 1 hr to a well shaken and cooled mixture of glycine (1·12 g, 15 mmoles), magnesium oxide (0·80 g), acetone (5 cc), and water (15 cc). The thick mixture was shaken at room temp for 1½ hr before being diluted with water (20 cc) and acidified with strong hydrochloric acid. Recrystallization, from water containing a few drops of methanol, of the crude product (2·05 g) obtained by

[24] F. Fichter and M. Schmid, *Helv. Chim. Acta* **3**, 704 (1920).
[25] R. H. Wiley, N. R. Smith and J. P. Johansen, *J. Amer. Chem. Soc.* **74**, 6298 (1952).

concentration and cooling, furnished *tosyl-α-methylalanylglycine* (1.70 g, 71%), m.p. 150–151° (Found: C, 49·65; H, 5·8; N, 8·7. $C_{12}H_{16}O_5N_2S$ requires: C, 49·7; H, 5·8; N, 8·9%).

Tosyl-α-methylalanylglycine ethyl ester

(a) Ethyl chloroformate (2·05 g, 20 mmoles) was added gradually to a solution, stirred at −5°, of tosyl-α-methylalanine (5·15 g, 20 mmoles) and triethylamine (2·05 g, 20 mmoles) in dry toluene (80 cc); the mixture set to a gel. After 30 min a solution of glycine ethyl ester hydrochloride (2·80 g 20 mmoles) and triethylamine (2·05 g) in dry dimethylformamide (50 cc) was added dropwise, and stirring at −2° was continued for 1½ hr. Next day the *dipeptide derivative* (1·65 g, 24%) was isolated in the usual way, m.p. 141–144° raised, by recrystallization from aqueous methanol, to 149–151° (Found: C, 52·4; H, 6·2; O, 23·7; N, 8·0. $C_{15}H_{22}O_5N_2S$ requires: C, 52·6; H, 6·5; O, 23·4; N, 8·2%).

(b) Glycine ethyl ester (2·48 g, 24 mmoles) was added to a solution of tosyl-α-methylalanine (3·08 g, 12 mmoles) in acetonitrile (100 cc). After a few min crystals separated. Dicyclohexyl carbodi-imide (2·48 g, 12 mmoles) was added and the mixture was shaken for 10 hr. The yield of dipeptide derivative, m.p. 142–146°, was 2·20 g (53%).

2-(1′-*Methyl*-1′-*toluene*-p-*sulphonamido*)*ethyloxazolone*

Application of the general method to tosyl-α-methylalanylglycine and recrystallization of the product from toluene furnished the *oxazolone* (61%), m.p. 172–173° (Found: C, 52·6; H, 5·4; N, 9·0. $C_{13}H_{16}O_4N_2S$ requires: C, 52·7; H, 5·4; N, 9·5%).

Tosyl-α-methylalanylglycyl-α-methylalanine methyl ester

A mixture of the foregoing oxazolone (0·266 g, 0·9 mmole), α-methylalanine methyl ester (0·212 g 1·8 mmoles), and dry acetone (10 cc) was kept for 30 min at room temp and then boiled for 30 min. Next day the solution was evaporated. Recrystallization, from ethyl acetate containing a trace of acetone, of the residue gave the *tripeptide derivative* (0·26 g, 70%), m.p. 193–194·5° (Found: C, 52·1; H, 6·8; N, 10·5. $C_{19}H_{27}O_6N_3S$ requires: C, 52·3; H, 6·6; N, 10·2%).

Tosyl-α,N-dimethylalanine

Dimethyl sulphate (7·5 g) and 4 N NaOH (12·5 cc) were added gradually during 1 hr to a shaken, cooled solution of tosyl-α-methylalanine (5·15 g) and sodium hydroxide (1·2 g) in water (30 cc). The mixture was shaken at room temp for 2½ hr further and then heated to 100° for 5 min. After removal of the precipitated solid (1·6 g), the product was obtained by acidification as an oil which slowly crystallized. Fractional crystallization from benzene and aqueous methanol afforded *tosyl-α,N-dimethylalanine* (2·68 g, 50%), m.p. 142·5–145° (Found: C, 52·8; H, 6·2; N, 5·1. $C_{12}H_{17}O_4NS$ requires: C, 53·1; H, 6·3; N, 5·2%).

Tosyl-α,N-dimethylalanyl chloride

Reaction, initially at room temp and after 2 hr at 45° for 10 min, between the foregoing acid and thionyl chloride, and recrystallization of the product from light petroleum (b.p. 60–80°) furnished *tosyl-α,N-dimethylalanyl chloride* (63%), m.p. 79–80° (Found: C, 50.0; H, 5.5;; N, 4·6. $C_{12}H_{16}O_3NSCl$ requires: C, 49·7; H, 5·6; N, 4·8%). Tosyl-α,N-dimethylalanine (88%) was recovered from hydrolysis of this acid chloride by sodium hydroxide in aqueous acetone.

Tosyl-α,N-dimethylalanyl-α-methylalanine

The foregoing acid chloride was reacted with α-methylalanine as in the preparation of tosyl-α-methylalanylglycine already described. The product, m.p. 112–160°, was a mixture of tosyl-α,N-dimethylalanine and the required *tosyl dipeptide*, which was separated through its insolubility in benzene and purified by recrystallization from aqueous methanol (yield about 8%), m.p. 210·5–212° (Found: C, 53·6; H, 6·8; N, 7·45. $C_{16}H_{24}O_5N_2S$ requires: C, 53·9; H, 6·8; N, 7·9%).

Tosyl-α-methylalanyl-α-methylalanine methyl ester

A solution of tosyl-α-methylalanyl chloride (2·76 g, 10 mmoles) in dry acetone (15 cc) was added in 3 portions to a cooled solution of α-methylalanine methyl ester (2·46 g, 21 mmoles) in acetone (20 cc).

Shaking was continued at room temp for 30 min before α-methylalanine methyl ester hydrochloride (1·33 g) was filtered off and the acetone evaporated. The *dipeptide derivative* (2.97 g, 83%), m.p. 146–147·5° (Found: C, 54·1; H, 6·9; N, 7·8. $C_{16}H_{24}O_5N_2S$ requires: C, 53·9; H, 6·8; N, 7·9%), crystallized from the concentrated ethyl acetate solution of the neutral product. When a mixture of α-methylalanine methyl ester hydrochloride (1·2 equivalents), triethylamine (2·4 equivalents), and dimethylformamide was brought into reaction with the acid chloride, the yield was only 71%.

Tosyl-α-methylalanyl-α-methylalanine

A solution of the foregoing ester (3·56 g, 10 mmoles) in 2 N NaOH (10 cc) was shaken at room temp during 4 hr. Acidification with dil hydrochloric acid furnished the *tosyl dipeptide* (3·41 g, 99%), m.p. 214–218° raised, by recrystallization from methanol, to 216–218° (Found: C, 52·6; H, 6·5; N, 8·4. $C_{13}H_{22}O_5N_2S$ requires: C, 52·6; H, 6·5; N, 8·2%).

4,4-*Dimethyl*-2-(1′-*methyl*-1′-*toluene*-p-*sulphonamido*)*ethyloxazolone* (II; $R = C_7H_7{\cdot}SO_2{\cdot}NH{\cdot}CMe_2$)

Recrystallization from light petroleum (b.p. 80–100°) of the product from application of the general method to the foregoing tosyl dipeptide furnished the *oxazolone* (94%), m.p. 140–141·5° (Found: C, 55·2; H, 6·3; N, 8·4. $C_{13}H_{16}O_4N_2S$ requires: C, 55·55; H, 6·2; N, 8·6%).

Tosyl-α-methylalanyl-α-methylalanyl-α-methylalanine methyl ester

A solution of the foregoing oxazolone (0·649 g, 2 mmoles) and α-methylalanine methyl ester (0·351 g, 3 mmoles) in acetonitrile (10 cc) was kept at 100° during 4 hr and then evaporated. Recrystallization of the residue from benzene–light petroleum furnished the *tripeptide derivative* (0·844 g, 95%), m.p. 156–158° (Found: C, 54·45; H, 7·1; N, 9·5. $C_{20}H_{31}O_6N_3S$ requires: C, 54·4; H, 7·1; N, 9·5%). An attempt to carry out the reaction under the conditions already described for tosyl-α methylalanylglycyl-α-methylalanine methyl ester was unsuccessful, and 80% of the oxazolone was recovered.

Tosyl-α-methylalanyl-α-methylalanyl-α-methylalanine

A solution of the foregoing ester (0·662 g, 1·5 mmoles) in 2 N NaOH (2 cc) was shaken at room temp during 5 hr and then acidified. The oil slowly crystallized, and recrystallization from aqueous methanol yielded the *tosyl tripeptide* (0·609 g, 89%), which was dried at 100°/0·1 mm to remove water of crystallization, m.p. 205–207° (Found: C, 53·1; H, 6.8; N, 9·4. $C_{19}H_{29}O_6N_3S$ requires C, 53·4; H, 6·8; N, 9·8%).

4,4-*Dimethyl*-2-(1′-*methyl*-1′-*tosyl*-α-*methylalanylamino*)*ethyloxazolone*
(II; $R = C_7H_7{\cdot}SO_2{\cdot}NH{\cdot}CMe_2{\cdot}CO{\cdot}NH{\cdot}CMe_2$)

The *oxazolone* (99%), m.p. 148–149° (Found: C, 56·1; H, 6·5; N, 10·0. $C_{18}H_{27}O_5N_3S$ requires: C, 55·7; H, 6·65; N, 10·3%), was obtained by recrystallization from benzene–light petroleum (b.p. 80–100°) of the product from the preceding tosyl-tripeptide.

Tosyl-α-methylalanyl-α-methylalanyl-α-methylalanyl-α-methylalanine methyl ester

A solution of the foregoing oxazolone (3·27 g, 8 mmoles) and α-methylalanine methyl ester (1·40 g, 12 mmoles) in acetonitrile (15 cc) was kept at 100° during 3 hr. When it was cooled most (3·05 g) of the product, m.p. 217–218°, crystallized and a second crop was obtained from the liquor by extraction of the neutral material. Recrystallization of the total from methanol afforded the *tetrapeptide derivative* (3·36 g, 80%), m.p. 218–219° (Found: C, 55·2; H, 7·3; N, 10·9. $C_{24}H_{38}O_7N_4S$ requires: C, 54·7; H, 7·3; N, 10·6%).

Tosyl-α-methylalanyl-α-methylalanyl-α-methylalanyl-α-methylalanine

When hydrolysis was carried out as already described for the tripeptide derivative, it was incomplete and 23% of the ester was recovered through its insolubility in sodium hydrogen carbonate solution. When this fraction had been treated again with sodium hydroxide, the combined yield of directly crystallized *tosyl tetrapeptide* was 87%, m.p. 260–262° (Found: C, 53·6; H, 6·9; N, 10·7. $C_{23}H_{36}O_7N_4S$ requires: C, 53·9; H, 7·1; N, 10·9%).

4,4-*Dimethyl*-2-(1′-*methyl*-1′-*tosyl*-α-*methylalanyl*-α-*methylalanylamino*)*ethyloxazolone* (II; R = $C_7H_7SO_2$·NH·CMe_2·CO·NH·CMe_2·CO·NH·CMe_2)

The *oxazolone* (95%), m.p. 224–225° (Found: C, 56·1; H, 6·9; N, 11·4. $C_{23}H_{34}O_6N_4S$ requires: C, 55·9; H, 6·9; N, 11·3%), was obtained by recrystallization from benzene of the product from the tosyl-tetrapeptide.

Tosyl-α-*methylalanyl*-α-*methylalanyl*-α-*methylalanyl*-α-*methylalanyl*-α-*methylalanine methyl ester*

(a) Trifluoroacetyl-α-methylalanyl-α-methylalanyl-α-methylalanine methyl ester (1·532 g, 4 mmoles) was treated with methanolic hydrogen chloride and then triethylamine as in its own preparation, and then 4,4-dimethyl-2-(1′-methyl-1′-toluene-*p*-sulphonamido)ethyloxazolone (1·296 g, 4 mmoles) was added to the acetonitrile solution. The mixture was boiled for 2 hr and then the neutral product was isolated. Recrystallization from aqueous methanol of the material which had crystallized from the concentrated ethyl acetate extract furnished the *pentapeptide derivative* (0·451 g, 19%), m.p. 251–252·5° (Found: C, 54·8; H, 7·3; N, 11·5. $C_{28}H_{45}O_8N_5S$ requires: C, 55·0; H, 7·4; N, 11·45%).

(b) α-Methylalanine methyl ester was combined with the foregoing oxazolone, derived from the tosyl tetrapeptide, just as with the oxazolone from the tosyl tripeptide, and the product (91%), m.p. 251°, was isolated in the same way. By this route the overall yield from tosyl dipeptide was 50%.

Derivatives of Formyl-α-*methylalanine*

Formyl-α-*methylalanine*

Acetic anhydride (160 cc) was added during 15 min to a stirred solution kept at 7–12° of α-methylalanine (20·6 g) in 98% formic acid (400 cc). The mixture was stirred at 15° for 30 min and at room temp for 2 hr. Finally it was diluted with ice-cold water (160 cc) and concentrated. Cooling to −10° and then recrystallization (at −10°) from water (25 cc) afforded the water-soluble *formyl*-α-*methylalanine* (20·0 g, 76%), m.p. 145–147° (Found: C, 46·0; H, 6·9; N, 10·75. $C_5H_9O_3N$ requires: C, 45·8; H, 6·9; N, 10·7%).

N-*Acetyl*-N-*formyl*-α-*methylalanine acetic anhydride* (IV)

Application of the general method for preparing oxazolones to formyl-α-methylalanine (2·62 g) and recrystallization of the product from benzene–light petroleum (b.p. 60–80°) furnished the *mixed anhydride* (IV) (2·58 g, 60%), m.p. 64–66°, ν_{max} 1815, 1764, 1686 cm^{-1} (Found: C, 50·4; H, 6·2; N, 6·7. $C_9H_{12}O_5N$ requires: C, 50·2; H, 6·1; N, 6·5%). The same compound (3·72 g 86%) was obtained from a mixture of formyl-α-methylalanine (2·62 g, 20 mmoles), triethylamine (2·02 g, 20 mmoles) and acetic anhydride (35 cc) which had been kept during 32 hr at room temp and then evaporated at low temp. Its alkaline hydrolysis at room temp afforded acetyl-α-methylalanine, recrystallized from water, m.p. 198–200·5° (reported[26] m.p. 196°) (Found: C, 49·4; H, 7·6; N, 9·9. Calc. for $C_6H_{11}O_3N$: C, 49·6; H, 7·6; N, 9·65%).

N-(*Isopropoxymethylene*)-α-*methylalanine methyl ester* (VI)

α-Methylalanine methyl ester (1·89 g, 12·3 mmole) and formimidoisopropyl ether hydrochloride[19] (1·52 g, 12·3 mmoles) were added at 0° to aqueous potassium hydroxide (2·7 ml of 25%) under ether (20 ml). After shaking at 0° for 10 min and at room temp for 30 min, the ether layer was decanted, the salt sludge washed twice with fresh ether, and the combined ether extracts washed with a little water, dried (Na_2SO_4) and evaporated. Distillation of the oily residue (1·1 g, 48%) yielded the *ester*, b.p. 57°/4 mm (Found: C, 57·9; H, 9·3; N, 7·5. $C_9H_{17}O_3N$ requires C, 57·7; H, 9·15, N, 7·5%).

4,4-*Dimethyloxazolone* (II, R = H)

Triethylamine (4·04 g, 40 mmoles) was added to a suspension of formyl-α-methylalanine (2·62 g, 20 mmoles) in carbon tetrachloride (40 cc), and the mixture was warmed until a clear solution was obtained. This solution was cooled in ice and shaken while thionyl chloride (2·38 g, 20 mmoles) in

[26] P. A. Levene and R. E. Steiger, *J. Biol. Chem.* **93**, 581 (1931); N. C. Hancox, *Aust. J. Sci. Res.* **3A**, 450 (1950).

carbon tetrachloride (10 cc) was added in 3 portions during 3 min. There was immediate precipitation of triethylamine hydrochloride and evolution of sulphur dioxide. After the mixture had been shaken without cooling during 5 min, the triethylamine hydrochloride (5·64 g) was removed by filtration. The solution of 4,4-dimethyloxazolone had major peaks in the infra-red spectrum (after compensation for solvent absorption) at 1850, 1638, 1202, 1104, 1008, 963, 917, 875 cm^{-1} and it could be fractionally distilled at 76° and atmospheric pressure without qualitative change of the spectrum, but there was a non-volatile residue. The solution decomposed gradually during storage.

For preparative purposes benzene is slightly preferable to carbon tetrachloride as the solvent, but neither ether nor petroleum ether could be substituted for carbon tetrachloride on account of the insolubility of formyl-α-methylalanine; xylene was tolerably satisfactory, but 4,4-dimethyloxazolone was not separated from it by fractional distillation at atmospheric pressure, during which decomposition occurred.

Formyl-α-methylalanine cyclohexylamide

Cyclohexylamine (4 g) was added to a cooled solution of 4,4-dimethyloxazolone in benzene (prepared from 2·62 g of formyl-α-methylalanine). After a few min the crystalline *cyclohexylamide* (3·77 g, 89%) began to separate and was recrystallized from aqueous methanol, m.p. 142–145° (softening at 136°) (Found: C, 62·4; H, 9·5; N, 13·4. $C_{11}H_{20}O_2N_2$ requires: C, 62·2; H, 9·5; N, 13·2%). The yield from a similar run in carbon tetrachloride was 87%.

1-*Cyclohexyl*-4,4-*dimethylimidazolone*

(a) A dry mixture of formyl-α-methylalanine cyclohexylamide (1·06 g, 5 mmoles) and tosyl-α-methylalanine (1·29 g, 5 mmoles) was heated gradually in a test-tube. At 170° evolution of bubbles began and it became rapid above 200°. Heating was continued to 230° when the *imidazolone* (0·88 g, 91%) sublimed; after resublimation at 120–140°/12 mm it had m.p. 110–113°, (Found: C, 67·85; H, 9·25; N, 14·2. $C_{11}H_{18}ON_2$ requires: C, 68·0; H, 9·3; N, 14·4%). Tosyl-α-methylalanine (0·97 g, 75%) was recovered by solution of the residue from the first sublimation in sodium hydrogen carbonate solution and subsequent acidification.

(b) A mixture of N-isopropoxymethylene-α-methylalanine methyl ester (0·375 g, 2 mmoles) and cyclohexylamine (0·20 g, 2 mmoles) was heated on the steam bath for 5 hr. The solid product obtained on cooling was recrystallized from ether to yield the imidazolone (0·282 g, 78%), m.p. 111–114°.

Formyl-α-methylalanylglycine ethyl ester

When a solution of glycine ethyl ester (2·83 g, 25 mmoles) in benzene (5 cc) was added to a solution of 4,4-dimethyloxazolone in benzene (prepared from 2·62 g, 20 mmoles, of formyl-α-methylalanine), there was slight evolution of heat and, after a few min, deposition of an oil. Next day, the supernatant solution was evaporated and the residue was reunited with the oil which had partially crystallized. Several extractions with hot benzene (20 cc portions) afforded *formyl-α-methylalanylglycine ethyl ester* (2·08 g, 47%), m.p. 102–103·5° (Found: C, 50·1; H, 7·3; N, 12·8. $C_9H_{16}O_4N_2$ requires: C, 50·0; H, 7·5; N, 13·0%). The insoluble residue was a gum, probably containing some amidine (III; $R' = CH_2{\cdot}CO_2Et$).

N,N′-*bis*(1-*Carboxy*-1-*methylethyl*)-*formamidine monomethyl ester* (III; $R' = CMe_2{\cdot}CO_2Me$)

A solution of α-methylalanine methyl ester (2·92 g, 25 mmoles) in benzene (5 cc) was added to a solution of 4,4-dimethyloxazolone in benzene (prepared from 2·62 g, 20 mmoles, of formyl-α-methylalanine). The oil, which soon began to separate, gradually crystallized, and next day the crystals (4·42 g), m.p. 132–137° (dec), were collected. Extraction with hot chloroform and dilution of the chloroform with benzene afforded the pure *amidine* (III; $R' = CMe_2{\cdot}CO_2Me$) (3·92 g, 85%), m.p. 145–146·5° (dec), ν_{max} 1742, 1709, 1570 or, in chloroform, 3175, 1736, 1709, 1634, 1558 (broad), 1513 (broad) cm^{-1} (broad absorption in region 2800–2600 cm^{-1} in both cases) (Found: C, 52·0; H, 7·9; N, 12·3. $C_{10}H_{18}O_4N_2$ requires: C, 52·2; H, 7·9; N, 12·2%). When hydrogen chloride was passed into a solution of the amidine in chloroform, heat was evolved and partial evaporation yielded the *hydro*-chloride, m.p. 155·5–156·5° (dec), p*Ka* 2·84, ν_{max} 3175, 1736, 1689, 1536 cm^{-1} (Found: C, 45·1; H, 7·2; N, 10·8; Cl, 13·3. $C_{10}H_{19}O_4N_2Cl$ requires: C, 45·1; H, 7·2; N, 10·5; Cl, 13·3%).

1-(1′-Carboxy-1′-methyl)ethyl-4,4-dimethylimidazol-5-one (V; R″ = H), *and its methyl ester* (V; R″ = Me)

(a) α-Methylalanine methyl ester (1·17 g, 10 mmoles) and ethyl orthoformate (0·50 g, 3·4 mmoles) were heated to reflux for 8 hr and allowed to stand overnight. Evaporation and crystallization of the residue from ether–light petroleum yielded the *imidazolone ester* (0·584 g, 81%), m.p. 87–92°, raised by recrystallization to 91·5–92·5° (Found: C, 56·6; H, 7·7; N, 12·9. $C_{10}H_{16}O_3N_4$ requires: C, 56·6; H, 7·6; N, 13·2%).

(b) The amidine (III; R′ = $CMe_2{\cdot}CO_2Me$, 2·30 g) was heated in a sublimation tube at 140° *in vacuo* for several hours. The loss in weight was 0·31 g; in a separate experiment conducted at atm press, the evolved methanol was collected and identified (infra-red spectrum). The subliming methyl ester (0·051 g, 2·5%) was collected, and after resublimation *in vacuo* had m.p. 88–91°. The involatile residue (1·93 g, 97%), m.p. 209–212°, crystallized from water as the *carboxylic acid monohydrate* (Found: C, 50·1; H, 7·5; N, 13·1. $C_9H_{14}O_3N_2{\cdot}H_2O$ requires: C, 50·0; H, 7·5; N, 13·0%). Drying at 100° and 0·5 mm press afforded the anhydrous *acid*, m.p. 211–212° (Found: C, 54·9; H, 7·1; N, 13·8. $C_9H_{14}O_3N_2$ requires: C, 54·5; H, 7·1; N, 14·1%). Diazomethane converted the acid to the above methyl ester (m.p. and mixed m.p. 88–91°).

Infra-red spectra of formamidines

Diphenylformamidine, (m.p. 139°), ν_{max} 1681, 1661, 1587, 1488, 1462. In chloroform, ν_{max} 3390 (weak), 1653, 1592, 1488. Diphenylformamidine hydrochloride (m.p. 248–250°), ν_{max} 3086, 1704, 1623, 1605, 1572, 1502, 1462 and 1456 cm^{-1}.

Dicyclohexylformamidine, dimorphic, form A (needles, m.p. 99–101°, Found: C, 75·0; H, 11·65; N, 13·1. Calc. for $C_{13}H_{24}N_2$: C, 74·9; H, 11·6; N, 13·45%). ν_{max} 3226, 3040, 1639 and 1548 cm^{-1}. In chloroform, ν_{max} 2907, 2857, 1658 and 1447 cm^{-1}. Form B (prisms, m.p. 100–102°) ν_{max} 3205, 3125 and 1689 cm^{-1}, (identical to form A in chloroform solution). Grundmann and Kreutzberger[27] give m.p. 106°. *Dicyclohexylformamidine hydrochloride*, m.p. 229–230° (dec) (Found: C, 63·8; H, 9·85; N, 11·8. $C_{13}H_{25}N_2Cl$ requires: C, 63·8; H, 10·3; N, 11·45%). ν_{max} 3165, 1695 and 1563 cm^{-1}.

Acknowledgements—This work was carried out during tenure of fellowships and a studentship from the British Council (M. T. L.), Parke, Davis and Co. (M. T. L.), and Monsanto Chemicals (D. S. J.). We wish to thank these bodies and also Parke, Davis and Co. for their generous support.

[27] C. Grundmann and A. Kreutzberger, *J. Amer. Chem. Soc.* 77, 6559 (1955).

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EXPERIMENTS ON THE SYNTHESIS OF SUBSTANCES RELATED TO TETRACYCLINES

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(*Received* 30 *December* 1959)

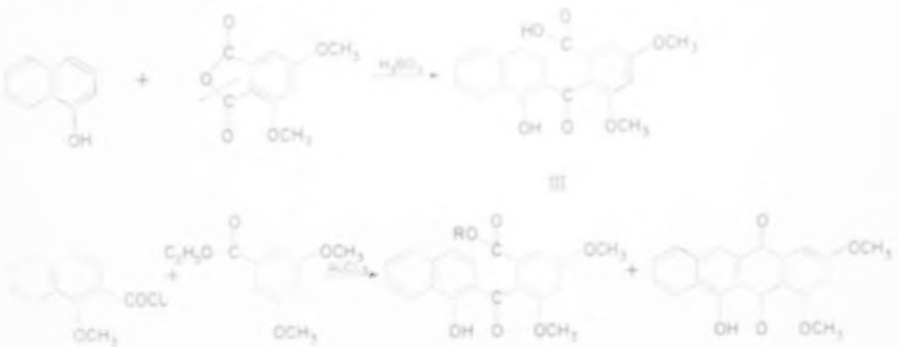
Abstract—The structures of tetracycline antibiotics are very complex. The total synthesis of these compounds, and of their degradation products such as anhydro-derivatives and desdimethylaminoterrarubein (I) would not only further contribute to the elucidation of their structures but also provide, in attempts at these syntheses, interesting findings concerning the chemistry of polycyclic compounds.

I

II

We have devised two possible routes for the synthesis of desdimethylaminoterrarubein (I) and the synthesis of 2,4,6-trihydroxy-5-oxo-5,12-dihydronaphthacene (II) was chosen as a model experiment.[1] Other synthetic experiments have also been directed toward the total synthesis of tetracycline and anhydrotetracycline.

CONDENSATION of α-naphthol with 3,5-dimethoxyphthalic anhydride in the presence of boric acid, gave 2-(α-hydroxy-β-naphthoyl)-3,5-dimethoxy benzoic acid (III) and Friedel–Crafts acylation of α-methoxy-β-naphthoyl chloride with ethyl-3,5-dimethoxybenzoate was shown to give three products, namely compounds III, IV and V.



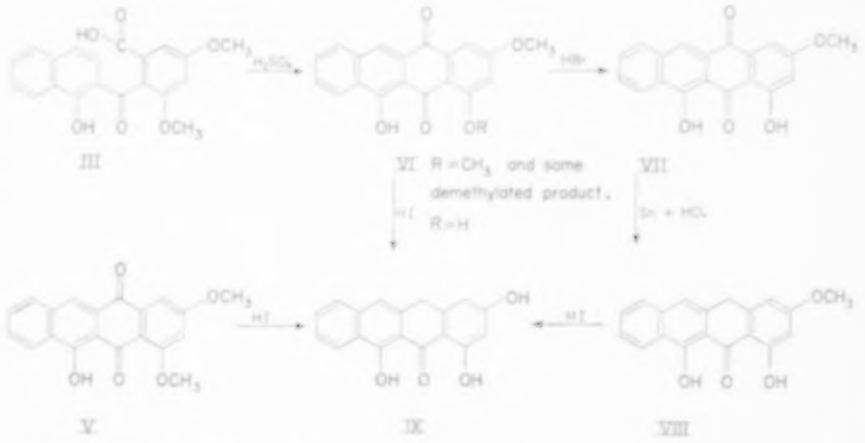
III R = H
IV R = C_2H_5

[1] Huang Yao-Tseng, Sheng Huai-Yu, Tai Li-Hsin and Tu Tung-Yuan, *Acta Chim. Sinica* **24**, 53 (1958).

The fact, that compound III was obtained from both routes, indicated that in the boric acid condensation, the anhydride linkage was split in the manner indicated by the broken line in the reaction formula, and in the Friedel–Crafts reaction, the methoxy group on the naphthalene ring was demethylated. It is of interest to note that compounds III, IV and V were obtained simultaneously from the Friedel–Crafts acylation reaction. Owing to partial demethylation, the product of the sulphuric acid cyclization of compound III was a mixture (VI), but the ultra-violet absorption spectrum of VI was almost identical with that of the compound V, evidently V was the cyclization product in the Friedel–Crafts reaction.

Treatment of V and VI separately with hydriodic acid gave rise to the same product, 2,4,6-trihydroxy-5-oxo-5,12-dihydronaphthacene (IX), m.p. 246° (decomp.) which possesses the basic structure of desdimethylaminoterrarubein (I).

The action of hydriodic acid on compound V is twofold, namely demethylation and the reduction of quinone to anthrone. In order to clarify this reaction mechanism, the mixture VI was treated with hydrobromic acid to demethylate the methoxy groups completely but leave the C_{12} keto group intact. In two runs, refluxed for 15 hr, the elementary analytical data and the methoxy group determination of the reaction product, showed that the product was a mono-methylated compound, 2-methoxy-4,6-dihydroxy-5,12-dioxo-5,12-dihydronaphthacene (VII). It was then reduced to VIII with tin and hydrochloric acid in acetic acid, a reagent which is commonly used for converting anthraquinone to anthrone. Treating VIII with hydriodic acid, furnished 2,4,6-trihydroxy-5-oxo-5,12-dihydronaphthacene (IX), identical with the compound previously obtained directly from compound V.

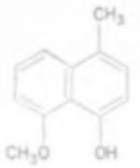


The assignment of the carbonyl group in our reduction product IX at C_5 but not at C_{12} was confirmed by the infra-red absorption spectra.[2] Compound VII showed a free carbonyl band at 1676 cm^{-1} and a hydrogen bonded carbonyl at 1613 cm^{-1}.[3] In compounds VIII and IX, there was no absorption in the region of 1650–1680 cm^{-1} but the bands expected for hydrogen bonded carbonyl groups were found in lower frequencies, in VIII at 1619 cm^{-1} and in IX at 1631 cm^{-1}. These are inconsistent with

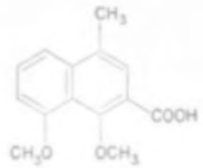
[2] Al. Steyermark and J. H. Gardner, *J. Amer. Chem. Soc.* **52**, 4887 (1930)
[3] M. St. C. Flett, *J. Chem. Soc.* 1441 (1948).

the assumption that C_{12} carbonyl was reduced. Except for a very strong hydroxy band at 3324 cm^{-1} found in IX, the absorption of any free hydroxy group had not been found in VII and VIII. Therefore, during the demethylation of mixture VI, it is the C_4 but not the C_2 methoxy group that was demethylated.

For the synthesis of desdimethylaminoterrarubein (I), two useful intermediates, namely 4-methyl-8-methoxy-naphthol-1 (X) and 1,8-dimethoxy-4-methyl-2-naphthoic acid (XI) have been prepared and their structures ascertained.[4]



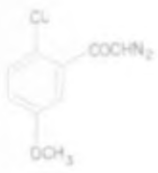
X



XI

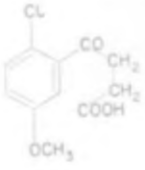
The synthesis of 4-methyl-8-methoxynaphthol-1 (X) was accomplished by two different routes. One consists of three stages: 1,8-naphthalenediol was methylated to give 8-methoxy naphthol-1 which was converted to 4-hydroxy-5-methoxynaphthaldehyde-1 by Gattermann aldehyde synthesis and then reduced into the requisite compound X by Huang-Minlon reduction.

Another synthesis of X consists of the following sequence of reactions: 2-chloro-5-methoxybenzoyl chloride was condensed with diazomethane to give the diazoketone

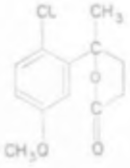


XII

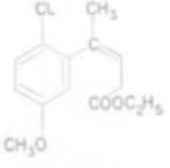
XIII



XIV



XV



XVI

XVII

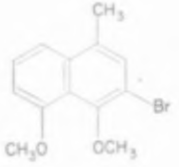
(XII) which was then treated with HCl or HBr to form phenacyl chloride (XIII, X=Cl) or bromide (XIII, X=Br) respectively. Either one was allowed to condense with diethyl sodiomalonate giving, after hydrolysis of the resulting ester, 2-chloro-5-methoxy phenacyl malonic acid, which in turn produced β-(2-chloro-5-methoxy

[4] Huang Yao-Tseng, Tsung Hui-Chuan, Tai Li-Hsin, Sheng Huai-Yu and Tu Tung-Yuan, *Acta Chim. Sinica* 24, 311 (1958).

benzoyl)-propionic acid (XIV) by pyrolysis. γ-Hydroxy-γ-(2-chloro-5-methoxyphenyl)-valerolactone (XV) was obtained by treating this acid with methyl magnesium bromide. The lactone afforded an unsaturated ester (XVI) by successive treatment with thionyl chloride, ethanol and finally by pyrolysis. Hydrogenation in the presence of Adams' catalyst followed by hydrolysis converted this unsaturated ester into γ-(2-chloro-5-methoxyphenyl)-valeric acid, the chloride of which was cyclized to 4-methyl-5-chloro-8-methoxytetralone-1 (XVII). Bromination of this compound with one mole of bromine gave 2-bromo-4-methyl-5-chloro-8-methoxytetralone-1. Dehydrobromination of this compound was effected readily by heating with morpholine on a water bath for 3 min giving 4-methyl-5-chloro-8-methoxynaphthol-1. Finally it was converted into 4-methyl-8-methoxy-naphthol-1 (X) by hydrogenolysis in the presence of Pd–$SrCO_3$ catalyst.

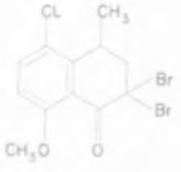
The behaviour of the product (X) obtained by two different routes was shown to be identical in all respects.

Another useful intermediate (XI) for the synthesis of desdimethylaminoterrarubein has been synthesized as follows. Compound X was first brominated to form 2-bromo-4-methyl-8-methoxynaphthol-1 which was then methylated, giving 2-bromo-4-methyl-1,8-dimethoxynaphthalene (XVIII). Successive treatment with n-butyl lithium and carbon dioxide converted it into compound XI.

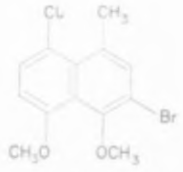


XVIII

The structure of XI was proved as follows: Bromination of 4-methyl-5-chloro-8-methoxytetralone-1 (XVII) with two moles of bromine afforded 2,2-dibromo-4-methyl-5-chloro-8-methoxytetralone-1 (XIX). It was converted into 1,8-dimethoxy-2-bromo-4-methyl-5-chloro-naphthalene (XX) when treated with sodium methoxide and dimethyl sulphate simultaneously.

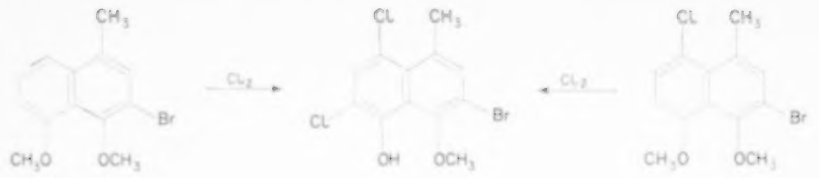


XIX



XX

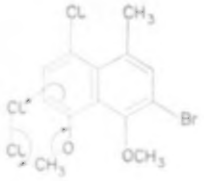
On the other hand, chlorination of 2-bromo-4-methyl-1,8-dimethoxy naphthalene (XVIII) produced, instead of the expected XX, 2,4-dichloro-5-methyl-7-bromo-8-methoxynaphthol-1 (XXI). Since XXI could also be obtained by chlorination of XX,



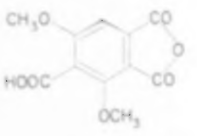
XVIII XXI XX

the location of bromine in XVIII was thus demonstrated and therefore the structure of XI ascertained.

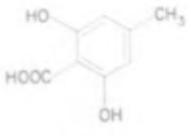
It was suggested that the formation of XXI may be attributed to the electrophilic attack of chlorine at the position *ortho* to methoxy group in the naphthalene ring with the concerted action of the chlorine ion on the methoxy group, thus resulting in simultaneous chlorination and demethylation.



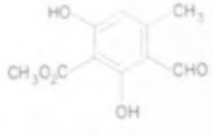
For the synthesis of desdimethylaminoterrarubein, another component, i.e. 3,5-dimethoxy-4-carboxyphthalic anhydride (XXII) has been prepared from orcinol by the following reactions.[5] Orcellinic acid (XXIII) prepared from orcinol was esterified to give its methyl ester which on formylation by Gattermann aldehyde synthesis afforded methyl 2,6-dihydroxy-3-formyl-4-methyl-benzoate (XXIV) in 95 per cent



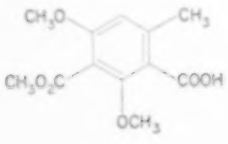
XXII



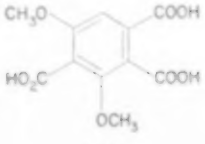
XXIII



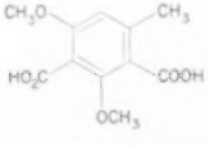
XXIV



XXV



XXVI



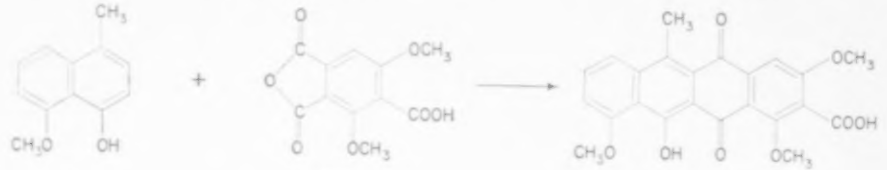
XXVII

yield. Methylation of the latter gave rise to methyl 2,6-dimethoxy-3-formyl-4-methyl benzoate, which on oxidation with potassium permanganate in neutral medium produced methyl 2,6-dimethoxy-3-carboxy-4-methyl-benzoate (XXV), while in alkaline medium produced two compounds: 3,5-dimethoxy-trimellitic acid (XXVI) m.p. 234–235° and 2,6-dimethoxy-4-methyl-isophthalic acid (XXVII). Either XXV or

[5] Huang Yao-Tseng, Tu Tung-Yuan and Tai Li-Hsin, *Acta Chim. Sinica* **24**, 322 (1958).

XXVII could be further oxidized to XXVI. The anhydride, 3,5-dimethoxy-4-carboxy-phthalic anhydride (XXII), was finally obtained by treating XXVI with acetic anhydride.

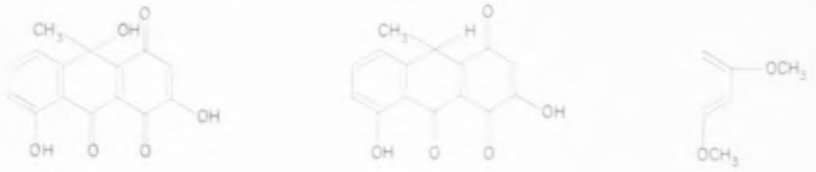
For the synthesis of desdimethylaminoterrarubein, preliminary experiment showed that the condensation product XXVIII can be obtained from X and XXII.[6]



X XXII XXVIII

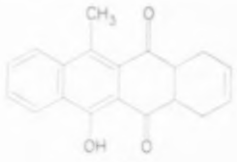
Other synthetic experiments have also been directed toward the total synthesis of tetracycline and anhydrotetracycline.

One possible synthetic route[7] which we devised involves the following steps, namely preparation of key intermediate compounds XXIX and XXX possessing the 1,4-anthraquinone structure, condensation of these compounds with suitable dienes such as derivatives of 1,3-dimethoxy-butadiene-1,3 (XXXI) and finally production of tetracycline or anhydrotetracycline analogue.



XXIX XXX XXXI

As a model experiment, the synthesis of 1,4,4a,5,12,12a-hexahydro-6-hydroxy-11-methyl-5,12-dioxonaphthacene (XXXII) has been achieved.

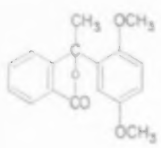


XXXII

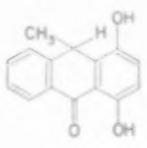
3-Methyl-3-(2′,5′-dimethoxyphenyl)-phthalide (XXXIII) was obtained by the action of 2-(2′5,-dimethoxy-benzoyl)-benzoic acid with methyl magnesium iodide. Reduction of this compound by means of zinc–sodium hydroxide followed by cyclization and demethylation afforded 1,4-dihydroxy-10-methyl-anthrone-9 (XXXIV), which on oxidation with lead tetra-acetate gave rise to crystalline 9,10-dihydro-9-oxo-10-methyl-anthraquinone-1,4 (XXXV) almost quantitatively. Condensation of the

[6] Huang Yao-Tseng, Tai Li-Hsin and Tu Tung-Yuan, unpublished.
[7] Huang Yao-Tseng, Nee Da-Nan, Hsu Yuen-Yao, Fung Hui-Min and Tsung Hui-Chuan, *Acta Chim. Sinica* **24**, 62 (1958).

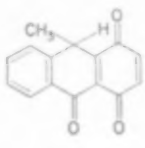
latter with 1,3-butadiene produced the requisite 1,4,4a,5,12,12a-hexahydro-6-hydroxy-11-methyl-5,12-dioxonaphthacene (XXXVI), m.p. 160–161°.



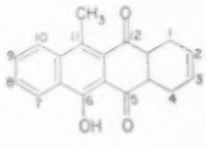
XXXIII



XXXIV

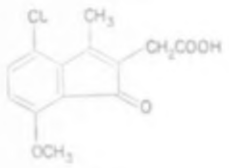


XXXV

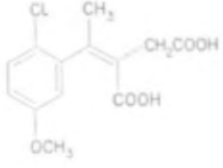


XXXVI

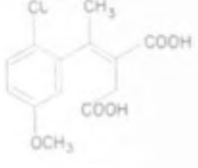
Another route to the synthesis of tetracycline or anhydrotetracycline has been started from the Stobbe condensation with 2-chloro-5-methoxy-acetophenone.[8] From the condensation product, two acids have been isolated, one melting at 157–158° and the other at 163–164°. Since the latter could be cyclized to an indenone derivative (XXXVII), it was assigned the structure XXXVIII and the acid (m.p. 157–158°) the structure XXXIX.



XXXVII

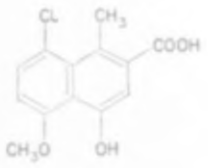


XXXVIII

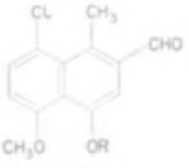


XXXIX

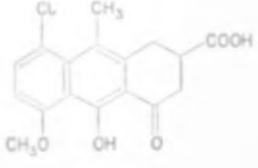
It is expected that, the acid XXXIX or its hydrogenated product would finally cyclize to a naphthalene derivative (XL) which on reduction would give a naphthaldehyde (XLI). Once more Stobbe condensation followed by reduction and cyclization would produce tetrahydroanthracene derivative (XLII) which would lead to anhydroaureomycin by a series of further treatments.



XL



XLI

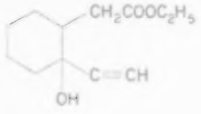


XLII

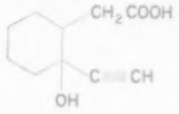
Since the structures of tetracyclines possess a 1,3-diketone system with an angular hydroxy group, we have devised a convenient method to synthesize the compound with such a structure feature and obtained satisfactory results.[9] Ethyl 2-ethynyl-2-hydroxycyclohexaneacetate (XLIII) and its corresponding acid (XLIV) were obtained by the ethynylation of ethyl cyclohexanone-2-acetate. Hydration of XLIII followed by

[8] Huang Yao-Tseng, Nee Da-Nan and Tang Ru-Yong, *Kexue Tongbao Scientia* 428 (1959).
[9] Huang Yao-Tseng and Hsu Yuen-Yao, *Acta Chim. Sinica* **24**, 47 (1958).

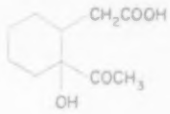
hydrolysis, gave 2-acetyl-2-hydroxycyclohexaneacetic acid (XLV). Its methyl ester was cyclized by sodium methoxide to form 9-hydroxydecaline-1,3-dione (XLVI) which showed characteristic concentration-dependent ultra-violet absorption spectra of 1,3-diketones. On the basis of the stability of the γ-hydroxy acids, XLIV and XLV, and



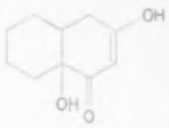
XLIII



XLIV



XLV



XLVI

the difficulty of lactonization of the latter, *cis* fusion of the two rings in compound XLVI is assigned.

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PLANT HORMONES—I

ISOLATION OF GIBBERELLIN A_1 AND GIBBERELLIN A_5 FROM *PHASEOLUS MULTIFLORUS*

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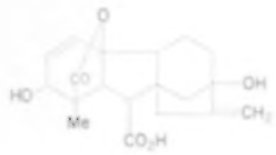
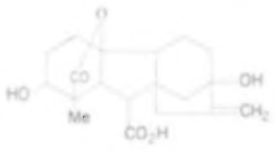
(*Received 5 June* 1960)

Abstract—The isolation of the growth-promoting acids, gibberellin A_1 and gibberellin A_5, from immature seed of *Phaseolus multiflorus* is described. The structure of gibberellin A_5 is established as V by degradation and by its preparation from gibberellin A_1.

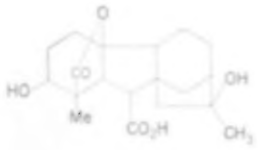
FOUR gibberellins have been isolated from the fungus, *Gibberella fujikuroi*: gibberellic acid (I), gibberellin A_1 (II), gibberellin A_2 (III), and gibberellin A_4 (IV).[1]



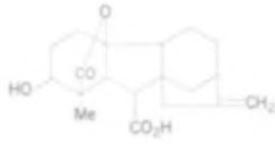
I



II



III



IV

The growth responses induced in plants by these fungal metabolites are essentially normal responses. This fact and other more specific arguments[2–4] led to the suggestion that the gibberellins or physiologically similar substances are growth-regulating hormones occurring in higher plants. This suggestion, supported by the isolation[1] from many plant sources of crude extracts with gibberellin-like biological properties, has now been confirmed by the isolation of two pure hormones, gibberellin A_1 (II) and a new gibberellin, gibberellin A_5 (V).

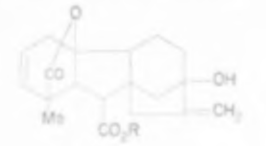
Since our brief note[5] on the isolation of gibberellin A_1 from immature seeds of *Phaseolus multiflorus*, this gibberellin has been isolated from seed of *P. vulgaris* by

[1] For review see P. W. Brian, J. F. Grove and J. MacMillan, *The Gibberellins*, in Zechmeister, *Prog. Chem. Org. Nat. Prod.* **18,** 350 (1960).
[2] M. Radley, *Nature, Lond.* **178,** 1070 (1956).
[3] P. W. Brian, *Symp. Soc. Exp. Biol.* **11,** 166 (1957).
[4] F. Lona, *Nuovo. G. Bot. Ital.* **63,** 61 (1956).
[5] J. MacMillan and P. J. Suter, *Naturwissenschaften* **45,** 46 (1958).

West *et al.*[6–8] and from water sprouts of *Citrus unshui* by Karawada and Sumiki[9]. In addition to gibberellin A_1, West *et al.* isolated a second active acid, bean factor II, which they were unable to characterize fully due to lack of material. Bean factor II is now known to be identical (West[8] and below) with gibberellin A_5 (V), a growth-promoting acid whose isolation from the seed of *P. multiflorus* has been briefly described[10] by us. We now wish to report our work in full.

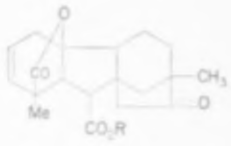
The extraction and purification procedures were followed by bio-assay using dwarf (Meteor) pea seedlings as described by Radley[11]. The crude acidic extract from immature seed of *P. multiflorus* was chromatographed on a column of celite-charcoal (cf. ref. 7) and was eluted stepwise with water containing increasing proportions of acetone. Elution with 55 per cent acetone in water gave gibberellin A_1 which was separated, by further chromatography on celite–silicic acid, from traces of an unknown acid, m.p. 207–209°. Gibberellin A_1 was identified by elementary analyses, infra-red spectrum, optical rotation and conversion to the methyl ester which was identified by mixed m.p. and infra-red spectrum. The melting point (Kofler) of gibberellin A_1 is variable, usually 256–260°, and is not a good criterion of purity; a higher melting modification, m.p. 285–287°, was obtained on one occasion. Gibberellin A_1 was isolated in a yield of about 2·0 mg per kilogram of fresh weight of seed.

Gibberellin A_5, m.p. 260–261°, $[\alpha]_D^{22}$ −77°, was eluted from the celite–charcoal column with 65–70 per cent acetone in water and was further purified by chromatography on celite–silicic acid; it was isolated in a total of 37 mg (ca 1·0 mg/kg of fresh weight of seed).

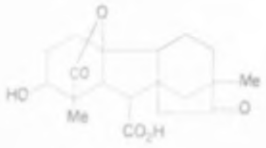


V, R=H
VI, R=Me

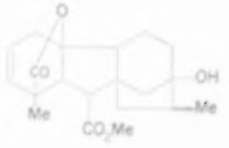
VII



VIII, R=H
IX, R=Me



X



XI

XII

Elementary analyses of gibberellin A_5 and its methyl ester (VI), m.p. 190–191°, $[\alpha]_D^{22}$ − 75°, indicated the molecular formula, $C_{19}H_{22}O_5$, for the acid. The infra-red spectrum of the acid showed absorption attributable to hydroxyl (3436 cm^{-1}), γ-lactone (1765 cm^{-1}), carboxylic acid (1734 cm^{-1}), exocyclic methylene (1659, 893 cm^{-1}) and *cis*-disubstituted olefinic (1624, 694 cm^{-1}) groupings. These assignments were confirmed by the infra-red spectrum of the methyl ester and account for all the oxygen functions.

[6] C. A. West and K. Murashige, *Plant. Physiol.* (Supplement) **33**, xxviii (1958).
[7] C. A. West and B. O. Phinney, *J. Amer. Chem. Soc.* **81**, 2424 (1959).
[8] C. A. West. Personal communication.
[9] A. Karawada and Y. Sumiki, *Bull. Agric. Chem. Soc. Japan* **23**, 343 (1959).
[10] J. MacMillan, J. C. Seaton and P. J. Suter, *Proc. Chem. Soc.* 325 (1959).
[11] M. Radley, *Ann. Bot.* **22**, 297 (1958).

The presence of two olefinic double bonds was confirmed by hydrogenation of the methyl ester which absorbed two molecules of hydrogen and gave a tetrahydro-derivative (VII), presumably (see ref.[1] and below) a mixture of C-8 epimers. Hydrogenation caused the disappearance of bands 1659, 1624 and 697 cm^{-1} and a marked decrease in intensity of the band at 893 cm^{-1}; these changes are consistent with the above olefinic assignments.

Treatment of gibberellin A_5 with dilute hydrochloric acid gave a keto-acid (VIII) showing absorption at 1740 cm^{-1}, ascribed to a saturated five-ring carbonyl group, in addition to bands at 1770 (γ-lactone) and 1695 (carboxylic acid) cm^{-1}; the methyl ester (IX) showed carbonyl absorption at 1775, 1734 and 1721 cm^{-1}. The acid VIII and methyl ester IX showed absorption bands at 674 and 678 cm^{-1} respectively, ascribed to a *cis*-disubstituted double bond. The rearrangement of gibberellin A_5 to a keto-acid (VIII) appears to be analogous to the Wagner–Meerwein rearrangement[12] of gibberellin A_1 (II) to the keto-acid (X).[13,14]

Boiling collidine converted the monomesylate of the C-8 epimeric mixture of methyl tetrahydrogibberellates into an unsaturated ester (XI) which showed two pairs of carbonyl bands in the infra-red and is presumably a C-8 epimeric mixture. Hydrogenation of XI afforded the methyl ester (VII) of tetrahydrogibberellin A_5; a slight difference in melting points and insignificant differences in the infra-red spectrum are ascribed to different proportions of C-8 epimers in the two samples. Gibberellin A_5 is thus a 2-deoxygibberellin A_1 containing a *cis*-disubstituted double bond.

The complete absence of hydrogenolysis products in the catalytic reduction of gibberellin A_5 methyl ester indicated the absence of a double bond allylic to the lactone hydroxyl function (cf. gibberellic acid[11]). The olefinic double bond was located as in V by dehydration of the methyl ester of the rearrangement product X of gibberellin A_1, both directly with phosphoric oxychloride and indirectly via the *p*-toluene-sulphonyl derivative. The methyl ester IX obtained was identical with the methyl ester of the rearrangement product VIII of gibberellin A_5; acidic hydrolysis of IX gave the free acid VIII. In addition to IX, treatment of the methyl ester of X with phosphorus oxychloride gave the corresponding 2-chloro-derivative.

Structure V for gibberellin A_5 was confirmed by dehydration of gibberellin A_1 via the methyl ester of the mono-*p*-toluene sulphonyl derivative. The product, gibberellin A_5 methyl ester, yielded gibberellin A_5 on alkaline hydrolysis.

The formation of the anhydro-derivatives IX and V from the appropriate sulphonic esters supports the revised structure I for ring A of gibberellic acid.[14,15] Kitamura *et al.*[16] have briefly reported ring A anhydro-derivatives of gibberellin A_2 and of methyl tetrahydrogibberellate and have assigned the structure XII to them. Our results show that these derivatives should be regarded as Δ^2-enes.

All compounds with a Δ^2-double bond show absorption maxima at 220–225 mμ (ε, 1400)—due possibly to trans-annular interaction between the double bond and

[12] J. F. Grove, J. MacMillan, T. P. C. Mulholland and W. B. Turner, *J. Chem. Soc.* 3049 (1960).
[13] N. Takahashi, Y. Seta, H. Kitamura, A. Karawada and Y. Sumiki, *Bull. Agric. Chem. Soc. Japan* **21**, 75 (1957).
[14] B. E. Cross, *J. Chem. Soc.* 3022 (1960).
[15] B. E. Cross, J. F. Grove, J. MacMillan, J. S. Moffatt, T. P. C. Mulholland, J. C. Seaton and N. Sheppard, *Proc. Chem. Soc.* 302 (1959).
[16] H. Kitamura, N. Takahashi, Y. Seta and Y. Sumiki, *Bull. Agric. Chem. Soc. Japan* **22**, 434 (1958).

the lactone carbonyl group—and show a large ΔM_D (−380) compared with the corresponding saturated compounds.

Gibberellin A_5 and the bean factor II, described by West and Phinney[7], have been shown to be identical by direct comparison of their infra-red spectra. Gibberellin A_5 also shows the same differential growth-promoting activity as bean factor II on the dwarf mutants, *d*-1, *d*-3, and *d*-5 of *Zea mais* (see Table 1).*

TABLE 1. RELATIVE ACTIVITIES OF GIBBERELLIC ACID, GIBBERELLIN A_5, AND BEAN FACTOR II FOR THE MUTANTS, *d*-1, *d*-3, AND *d*-5 OF *Zea mais*

Mutant of *Zea mais*	Gibberellic acid	Gibberellin A_5	Bean factor II
d-1	100	10	5
d-3	100	500	300
d-5	100	100	90

EXPERIMENTAL

The following chromatographic materials were used: activated charcoal (B.D.H.), silica gel M.F.C. (Hopkins and Williams), and celite 545 (Johns–Mandeville). Unless otherwise stated, ultraviolet spectra were determined in ethanol, optical rotations in methanol, and infra-red spectra as "Nujol" mulls using a Grubb–Parsons G.S.2 spectrophotometer. "Light petroleum" refers to the fraction of b.p. 60–80°.

By the term "worked up as usual" is meant washed successively with dil hydrochloric acid, sodium hydrogen carbonate solution, and water, dried with sodium sulphate and evaporated.

Extraction

Immature seed (87·3 kg) of *Phaseolus multiflorus* were deep-frozen and then extracted with 70% aqueous ethanol (2 × 40 l.) for 24 hr at room temp. The filtered extract was concentrated at 40–50° in a climbing film evaporator and the aqueous concentrate (3·0 l.; pH 5·4), after adjustment to pH 3 with 2 N HCl, was extracted with ethyl acetate (12 × 1 l.). Concentration of the ethyl acetate extract to ca. 500 ml gave fumaric acid (8·0 g), identified by m.p. and infra-red spectrum after sublimation at 150°/10^{-3} mm and crystallization from water. The ethyl acetate mother liquors were then extracted with phosphate buffer (20 × 100 ml, pH 6·2), washed with water, dried, and evaporated giving a biologically inactive gum (37·5 g). The phosphate buffer extract, after adjustment to pH 3 with 3 N HCl (360 ml), was extracted with ethyl acetate (14 × 250 ml) which, on recovery, gave a biologically-active acidic gum (14·6 g). Attempted preparation of a crystalline cyclohexylamine salt, by addition of cyclohexylamine to the acidic gum in acetone, produced a gum; dissolution of the latter in water, acidification with 3 N HCl, and recovery in ethyl acetate gave a gum (12·0 g) which is referred to below as the *crude acidic extract*.

Chromatography

A. *Celite:charcoal.* The crude acidic extract (1·0–2·0 g) was adsorbed on silicic acid (5·0 g) by evaporation of an acetone solution and placed on top of a column (40 × 3 cm) of celite (60 g): charcoal (30 g). The column was eluted in 200 ml fractions, first with water then with water containing acetone increasing in 5% steps. Bio-assay showed that fraction 12, eluted with 55% acetone, possessed most of the biological activity.

These fractions were worked up by evaporation of the acetone and extraction of the aqueous residue with ethyl acetate (4 × 50 ml); recovery gave gums which were further chromatographed as follows.

B. *Celite: silicic acid.* The fractions from (A), adsorbed on silicic acid (2·0 g), were placed on

* We are grateful to Dr. C. A. West and Professor B. O. Phinney, University of California, Los Angeles, for making the comparisons of gibberellin A_5 and bean factor II and for their permission to quote these results.

top of a column (18 × 1·5 cm) of celite (10 g):silicic acid (5 g) and eluted in 50 ml fractions of chloroform containing ethyl acetate increasing in 5% steps.

Isolation of gibberellin A_1. Fraction 12 (40–50 mg), obtained as in A from the crude acid extract (1·0 g), crystallized from ethyl acetate—light petroleum in ill-defined plates or prisms (15–18 mg) m.p. 256–260° (decomp), of gibberellin A_1. (Found: C, 65·3; H, 6·9%; equiv. (potentiometric), 354. Calc. for $C_{19}H_{24}O_6$: C, 65·5; H, 6·9%; M, 348); $[\alpha]_D^{21}$ +35° (*c*, 1·02 in ethanol). The infra-red spectrum was identical with that of an authentic specimen. The methyl ester, prepared with diazomethane, had m.p. and mixed m.p. 232–234° and showed infra-red absorption identical with that of an authentic specimen.

Fractions 12, from 3·5 g crude acidic extract, and from which gibberellin A_1 had been removed by crystallization were combined with the total fractions 12 from 3·5 g of crude acidic extract, and were chromatographed on celite:silicic acid as in B. The following fractions were collected:

(1) 10% ethyl acetate eluted azelaic acid (5·0 mg) m.p. and mixed m.p. 100–103°.

(2) 20–30% ethyl acetate gave a solid which crystallized from ether in prisms (2·0 mg) m.p. 207–209° of an unidentified acid; ν_{max} 3480, ca. 2700, 1718, 1684, ca. 1670, 1637, 1610 cm^{-1}. (Perkin–Elmer Infracord 137); λ_{max} 259 ($E_{1cm}^{1\%}$ 964).

(3) 40–50% ethyl acetate eluted gibberellin A_3, crystallizing from acetone—light petroleum in prisms (33 mg) m.p. 285–287°; recrystallization from the same solvent, and seeding with a specimen m.p. 235–240°, gave prisms m.p. 250–255°; seeding the crystallization of the latter with the form m.p. 285–287° did not raise the m.p.; all forms had the same infra-red spectrum (Perkin–Elmer Infracord 137).

Isolation of gibberellin A_5. The combined fractions 14 (195 mg), from the chromatography of 4·0 g crude acidic extract as in A, were rechromatographed as in B. After elution with 50 ml chloroform and 50 ml 5% ethyl acetate, elution with 10% ethyl acetate (4 × 50 ml) afforded *gibberellin* A_5, crystallizing from acetone–light petroleum in prisms (27 mg) m.p. 260–261° (for characterization and degradation see below).

The combined fractions 15 (301 mg) from 7·0 g crude acidic extract were re-chromatographed as in B. Elution with 50 ml of 5 and 10% ethyl acetate and crystallization of the recovered gum from ether gave gibberellin A_6 as prisms (10 mg) m.p. 256–260°.

Gibberellin A_5: *derivatives and degradation*

Gibberellin A_5 (V). Gibberellin A_5 crystallized from ether or acetone–light petroleum in colourless prisms m.p. 260–261°, $[\alpha]_D^{27}$ − 77° (*c*, 0·5) (Found: C, 68·7; H, 7·1. $C_{19}H_{22}O_5$ requires: C, 69·1; H, 6·7%): ν_{max} 3436, 2700 (broad), 1765, 1734, 1659, 1624, 893 and 694 cm^{-1}: λ (shoulder) 225 mμ, (log ε 3·15).

Gibberellin A_5 *methyl ester* (VI). Excess ethereal diazomethane was added to a solution of gibberellin A_5 in methanol. The *methyl ester*, obtained by evaporation, crystallized from ether or acetone—light petroleum in prisms m.p. 191–193°, $[\alpha]_{25}^{D}$ −75° (*c*, 0·5) (Found : C, 69·8; H, 7·2. $C_{20}H_{24}O_5$ requires: C, 69·75; H, 7·0%); ν_{max} 3475, 1754, 1730, 1659, 1624, 893 and 697 cm^{-1}, λ (shoulder) 225 mμ (log ε 3·28).

Hydrogenation of gibberellin A_5 *methyl ester* (VII). The methyl ester (4·23 mg) in glacial acetic acid (5 ml) with Adams' catalyst absorbed 0·57 ml hydrogen at 25° and 740 mm Hg (= 1·8 double bonds). After filtration, the solvent was evaporated and the *tetrahydro-derivative* (VII; probably a C-8 epimeric mixture) crystallized from ether–light petroleum in rods (4·0 mg) m.p. 205–207°, $[\alpha]_D^{25}$ +30° (*c*, 0·35); ν_{max} 3571, 1774, and 1706 cm^{-1}. For analyses see following section.

Treatment of gibberellin A_5 *with dilute hydrochloric acid.* Gibberellin A_5 (9·5 mg) in ethanolic hydrochloric acid (1·0 ml) (ethanol:water:concentrated hydrochloric acid, 3:2:1) was heated at 100° for 2·5 hr. After evaporation of the solvent *in vacuo*, the residue was crystallized from acetone–light petroleum giving the *keto-acid* (VIII) as prisms (2 mg) m.p. 263–265°; ν_{max} 1770, 1740, 1695, 674 cm^{-1}; λ_{max} 221, 275 mμ (log ε 3·17 and 2·0). For analyses see following section. *Esterification* with diazomethane gave the *methyl ester* (IX) which crystallized from ether–light petroleum in prisms m.p. 158–160°; ν_{max} 1775, 1734, 1721, 678 cm^{-1}. For analyses see following section.

Preparation of gibberellin A_5 *and its derivatives from gibberellin* A_1

The monomethane sulphonate of the methyl tetrahydrogibberellates (C-8 *epimeric mixture*). The mixture of C-8 epimers (200 mg) and methane sulphonyl chloride (0·1 ml) in pyridine (25 ml) were

allowed to stand at room temp for 65 hr. The solvent was evaporated under reduced pressure and the residue was dissolved in ethyl acetate which was worked up as usual. The residue was added to a column of alumina (16 × 1·5 cm) in benzene and eluted with benzene containing increasing proportions of chloroform giving (i) 1:1 benzene:chloroform; a colourless gum (80 mg); (ii) 45:55 benzene:chloroform; the *monomethane sulphonate* crystallizing from acetone–light petroleum in prisms (60 mg) m.p. 194–197° (Found: C, 56·9; H, 6·8. $C_{21}H_{30}O_8S$ requires: C, 57·1; H, 6·8%); ν_{max} 3559, 1778, 1724, 1351, 1176, 935 cm^{-1}.

The anhydro-ester (XI). The above monomethane sulphonate (20 mg) was refluxed in dry collidine for 6 hr. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate and was worked up as usual. The crystalline residue when recrystallized from acetone–light petroleum gave the *anhydro-ester* (XI) as prisms (10 mg) m.p. 180–185° (Found: C, 69·1; H, 7·6. $C_{20}H_{26}O_5$ requires: C, 69·3; H, 7·6%), ν_{max} 3525, 3505, 1777, 1762, 1734, 1714 cm^{-1}; λ_{max} 221 mμ, (log ε 3·12).

Hydrogenation of the anhydro-ester (XI). The anhydro-ester (17·44 mg) in glacial acetic acid (5 ml) with Adams' catalyst absorbed 1·04 ml of hydrogen at N.T.P. (0·9 double bonds). The solution was filtered, the solvent was removed, and the residue was crystallized from ether–light petroleum giving rods m.p. 212–215°, $[\alpha]_D^{21}$ +27° (*c*, 0·37) (Found: C, 68·65; H, 8·35. $C_{20}H_{28}O_5$ requires: C, 68·9; H, 8·1%), identical (mixed m.p. and infra-red spectrum) with tetrahydrogibberellin A_5 methyl ester.

The p-*toluene sulphonate of the keto-ester*. The keto-ester (X, 350 mg) and *p*-toluene sulphonyl chloride (250 mg) were allowed to stand in dry pyridine (10 ml) for 80 hr. The solvent was evaporated under reduced pressure and the residue was dissolved in ethyl acetate and worked up as usual. The crystalline residue was recrystallized from acetone–light petroleum giving the *p-toluene sulphonate* as needles (245 mg) m.p. 208–210° (Found: C, 62·5; H, 6·4. $C_{27}H_{32}O_8S$ requires: C, 62·8; H, 6·2%): ν_{max} 1789, 1739, 1597, 1370, 935 cm^{-1} (Infracord).

The anhydro-keto-ester IX. (a) The *p*-toluene sulphonate (100 mg) was refluxed in collidine (10 ml) for 6 hr. The solvent was evaporated under reduced pressure and the residue dissolved in ethyl acetate and worked up as usual. Crystallization of the residue from acetone–light petroleum gave the *anhydro-keto-ester* (IX) as prisms (60 mg) m.p. 160–164° $[\alpha]_D^{19}$ −55° (*c*, 0·8) (Found: C, 69·6; H, 7·1. $C_{20}H_{24}O_5$ requires: C, 69·75; H, 7·0%) identical (mixed m.p. and infra-red spectrum) with the methyl ester IX of the acid VIII, obtained by treatment of gibberellin A_5 with dilute hydrochloric acid.

(b) The keto-ester (X, 180 mg) was dissolved in pyridine (10 ml) and refluxed with phosphorus oxychloride (3 ml) for 2 hr. After cooling the solution was poured over ice and extracted with ethyl acetate. The extract was worked up as usual. Fractional crystallization of the residue from acetone–light petroleum gave (i) fine needles (30 mg) m.p. 225° (Found: C, 62·9; H, 6·6; Cl, 9·35. $C_{20}H_{25}O_5Cl$ requires: C, 63·1; H, 6·6; Cl, 9·1%, (ii) prisms (90 mg) m.p. 160–164° identical (mixed m.p. and infra-red spectrum) with the anhydro-keto ester IX. *Hydrolysis* of the ester IX with boiling hydrochloric acid for 2 hr gave the keto-acid VIII which crystallized from acetone–light petroleum in prisms m.p. 264° $[\alpha]_D^{19}$ −61° (*c*, 0·6) (Found: C, 68·55; H, 6·8. $C_{19}H_{22}O_5$ requires: C, 69·1; H, 6·7%) identical (mixed m.p. and infra-red spectrum) with the acid VIII, obtained by treatment of gibberellin A_5 with dilute hydrochloric acid. *Hydrogenation* of the ester IX (15·0 mg) in glacial acetic acid (5 ml) with a palladium–charcoal catalyst gave the *dihydro*-derivative, crystallizing from acetone–light petroleum in prisms m.p. 190–191°, $[\alpha]_D^{19}$ +50° (Found: C, 69·0; H, 7·6. $C_{20}H_{26}O_5$ requires: C, 69·3; H, 7·6%).

p-*Toluene sulphonation of gibberellin* A_1 *methyl ester*. Gibberellin A_1 methyl ester (500 mg) and *p*-toluene sulphonyl chloride (300 mg) were dissolved in pyridine (5 ml) and allowed to stand for 50 hr. Ethyl acetate was added and the solution was worked up as usual. The residue was added to an alumina column (16 × 1·5 cm) in benzene and eluted with benzene containing increasing proportions of chloroform giving (i) 9:1 benzene:chloroform, the *di*-p-*toluene sulphonate* as a glass (120 mg) (Found: C, 61·15; H, 5·6. $C_{34}H_{38}O_{10}S$ requires: C, 60·9; H, 5·8). (ii) 4:1 benzene:chloroform, the *mono*-p-*toluene sulphonate* as a glass (322 mg) (Found: C, 62·8; H, 6·3. $C_{27}H_{32}O_8S$ requires: C, 62·8; H, 6·2%) (iii) 1:1 benzene:chloroform, gibberellin A_1 methyl ester (70 mg) m.p. 234°.

Gibberellin A_1 *methyl ester*. The above mono-*p*-toluene sulphonate (300 mg) was heated under reflux in collidine (10 ml) for 5 hr. The neutral product was crystallized from acetone–light petroleum

giving *gibberellin* A_8 *methyl ester* (VI) as prisms (98 mg) m.p. 191–192°, $[\alpha]_D^{21} -79°$ (*c*, 0·63) (Found: C, 69·8; H, 7·3%).

On hydrogenation in glacial acetic acid with Adams' catalyst, the ester absorbed 1·9 moles hydrogen giving tetrahydrogibberellin A_8 methyl ester (probably the C-8 epimeric mixture) which crystallized from acetone–light petroleum in prisms m.p. 206–208°.

Gibberellin A_8. Gibberellin A_8 methyl ester (70 mg) was dissolved in methanol (2 ml) and heated at 100° for 2 hr with aqueous potassium hydroxide (2 ml of 10%). Water was added and the methanol was removed under reduced pressure. The resulting solution was washed with ethyl acetate, acidified with dil. hydrochloric acid and extracted with ethyl acetate. After drying (sodium sulphate) the extract was evaporated and residue crystallized from ether giving gibberellin A_8 as prisms (20 mg) m.p. 260–261° $[\alpha]_D^{21} -76°$ (*c*, 0·64) (Found: C, 69·0; H, 6·9%).

Acknowledgements—We thank Dr. P. W. Brian for his encouragement in initiating this work; Miss M. Radley for the bio-assays: Dr. J. R. Bartels-Keith and Mr. M. B. Lloyd for the infra-red spectra; and numerous colleagues for their help in obtaining the immature seed of *P. multiflorus*.

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TERPENOIDS AND RELATED COMPOUNDS—II[1]

INVESTIGATIONS ON THE STRUCTURE OF NIMBIN[2]

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Abstract—Nimbin, the crystalline principle of *M. azadirachta* Linn. is assigned the molecular formula $C_{28}H_{36}O_9$. 1,2,5-Trimethylnaphthalene was isolated from the dehydrogenation of a reduction product of nimbin. The products of alkaline degradation and pyrolytic experiments establish that nimbin possesses either of the partial structures X or XI.

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IN a previous communication[1] we reported investigations on the constituents of the trunk bark of *Melia azadirachta* Linn. and the structure of nimbiol, the new keto-phenol isolated. The present communication deals with investigations on nimbin, the bitter principle of the tree, isolated by Siddiqui *et al.* from the seed-oil,[3] the blossoms,[4] the root bark[5] and the trunk bark[6] and given the molecular formula, $C_{28}H_{40}O_8$. Later Mitra[7] suggested the molecular formula, $C_{28}H_{38}O_8$ ($\pm CH_2$) for nimbin, and isolated acetic acid, methanol, nimbinic acid, m.p. 263°, Neutral A or desacetyl nimbin, m.p. 215° and nimbic acid, m.p. 160–162° from the alkaline hydrolysis. Nimbinic acid on esterification gives Neutral A, which on acetylation gives nimbin. Mitra[7] suggested the presence of (a) an aldehyde, (b) an acetoxy, (c) a carbomethoxy, (d) an $\alpha\beta$-unsaturated lactone and (e) an isolated methoxy group in nimbin. Narasimhan[8] on the other hand suggested the molecular formula $C_{30}H_{36}O_9$ and agreed that nimbin has an acetoxy, a carbomethoxy and an isolated methoxy group and further suggested that nimbin has an $\alpha\beta$-unsaturated ketone, another $\alpha\beta$-unsaturated carbomethoxy group as well as a furan ring. On hydrogenation nimbin gives dihydronimbin and tetrahydronimbin. This worker further established that in dihydronimbin the ethylenic linkage in conjugation with the ketonic carbonyl group has been hydrogenated. An investigation on the nimbic acid of Mitra led Narasimhan to suggest that this acid is dibasic, and on sublimation loses water and carbon dioxide to give an enol-lactone, 'pyronimbic acid'. Later Mitra[9] provisionally suggested a 1-carbomethoxy steroid type structure for nimbin without apparent reason.

In continuation of the work on *M. azadirachta* Linn.[1] we selected the trunk bark as the source of nimbin. The neutral fraction of the benzene extract of the trunk bark was subjected to partition between petroleum ether and 80 per cent aqueous methanol.[1] The methanolic extract on acetylation and chromatography yielded nimbin, m.p. 204–205°, $[\alpha]_D$ +168°, in ca. 0·08% yield. The bitterness of nimbin is very mild, whereas that of its various derivatives is quite strong.

[1] Part I: P. Sengupta, S. N. Choudhuri and H. N. Khastgir, *Tetrahedron* **10**, 45 (1960).
[2] Preliminary investigations on nimbin were published in short communications: [c] P. Sengupta, S. K. Sengupta and H. N. Khastgir, *Chem & Ind.* 1402 (1958); [b] 397 (1959) and [c] 1194 (1959).
[3] S. Siddiqui, *Curr. Sci.* **11**, 278 (1942).
[4] C. Mitra, P. N. Rao, S. Bhattacharjee and S. Siddiqui, *J. Sci. & Ind. Res. India* **6B**, 19 (1947).
[5] C. Mitra, P. N. Rao and S. Siddiqui, *J. Sci. & Ind. Res. India* **12B**, 152 (1953).
[6] S. Bhattacharjee, C. Mitra and S. Siddiqui, *J. Sci. & Ind. Res. India* **12B**, 154 (1953).
[7] C. Mitra, *J. Sci. & Ind. Res. India* **15B**, 425 (1956).
[8] N. S. Narasimhan, *Chem. & Ind.* 661 (1957).
[9] C. Mitra, *J. Sci. & Ind. Res. India* **16B**, 477 (1957).

The analytical data of nimbin and its degradation products suggest the molecular formula, $C_{29}H_{36}O_9$ and indicate the presence of two methoxy groups in the molecule, in agreement with the observation of Mitra[7], but in contrast to the observation of Narasimhan[8]. The ultra-violet absorption spectra of nimbin show two maxima, one at 210 mμ, which may be a composite one of isolated chromophores, an $\alpha\beta$-unsaturated ketone, a furan and one or two ethylenic linkages, while the second one at 330 mμ is due to the $\alpha\beta$-unsaturated ketone.[8] In the infra-red spectra nimbin shows peaks at 1687 ($\alpha\beta$-unsaturated ketone), 1730 (esters and acetate) and 1510 and 875 cm^{-1} (β-substituted furan[10,11]). The ultra-violet absorption spectra of dihydronimbin,[8] $C_{29}H_{38}O_9$ show two maxima, at 210 mμ and 298 mμ and the infra-red spectra show peaks at 1740 (carbonyl) and 1500 and 872 cm^{-1} (β-substituted furan).

Both nimbin and dihydronimbin show infra-red peaks around 1245 cm^{-1} indicating the presence of acetoxy groups. These groups could not be determined due to decomposition and frothing, but on hydrolysis the acetic acid generated was identified as *p*-bromophenacyl ester.

On heating under reflux with methanolic potassium hydrogen carbonate, nimbin gives nimbinic acid,[7] $C_{28}H_{32}O_8$, m.p. 259–261°d, which shows infra-red peaks at 3420 (hydroxyl), 1743, 1718 and 1677 (carbonyl) and 1505 and 875 cm^{-1} (furan). On titration it is found to be monocarboxylic and on esterification it gives methyl nimbinate, $C_{27}H_{34}O_8$, m.p. 215–216° which on acetylation gives nimbin. Thus nimbinic acid is formed from nimbin by the hydrolysis of an acetoxy and a carbomethoxy group. The infra-red spectra of methyl nimbinate show peaks at 3420 (hydroxyl), 1730, 1715 and 1680 (carbonyl) and 1505 and 875 cm^{-1} (furan).

In addition to these infra-red peaks, nimbinic acid and methyl nimbinate show peaks at 1225 and 1230 cm^{-1} respectively, which led to the erroneous conclusion[2b] that nimbin has yet another acetoxy group. But as work progressed, we agreed[2c] with Narasimhan that nimbin has one acetoxy group and two carbomethoxy groups.

Nimbic acid prepared according to the method of Narasimhan melted at 185°d instead of 160–161°d as reported by him. A sample of nimbic acid supplied by Dr. Narasimhan after drying melted at 185°d. On esterification this acid gives methyl nimbate or desacetyl nimbin, $C_{27}H_{34}O_8$[2c] which is identical with our methyl nimbinate. Thus we agree with Narasimhan regarding the functions of eight out of the nine oxygen atoms of nimbin. These are a β-substituted furan, an acetoxy, two carbomethoxy and an $\alpha\beta$-unsaturated ketone groups. We do not agree with the view[8] that the ninth oxygen atom is present in an isolated methoxy group. Nimbin shows the presence of two methoxy groups that are accounted for by the presence of two carbomethoxy groups in the molecule.

Nimbin on reduction with lithium aluminium hydride yields a gummy product ($\lambda_{max.}$ 206 mμ), which did not crystallize even after acetylation and chromatography. The gummy product on dehydrogenation[2b,c] with selenium, gives 1,2,5-trimethylnaphthalene identified by its ultra-violet absorption spectra and by melting point and mixed melting point of its 1,3,5-trinitrobenzene adduct with that of an authentic specimen. Independently, however, Narasimhan[12] isolated presumably the same

[10] T. Kubota, *Tetrahedron* **4**, 68 (1958).
[11] F. M. Dean and T. A. Geissman, *J. Org. Chem.* **23**, 596 (1958).
[12] N. S. Narasimhan, *Ber. Dtsch. Chem. Ges.* **92**, 769 (1959).

naphthalene derivative, which he suggested, is 1,2,5- or 1,4,5-trimethylnaphthalene. The isolation of 1,2,5-trimethylnaphthalene indicates that nimbin is probably dicarbocyclic.

Nimbin on standing with cold methanolic potassium hydroxide gives only nimbic acid,[8] but on heating under reflux with methanolic alkali, it gives a mixture of acids from which no single component could be crystallized. The acid mixture was esterified and after chromatography over alumina yielded three crystalline esters,[2] (i) Ester A, m.p. 138–139°, $[\alpha]_D$ +130°,(ii) Ester B, m.p. 153–154°, $[\alpha]_D$ +140° and (iii) Ester C, m.p. 158–160°, $[\alpha]_D$ +302°. The Esters A, B and C show molecular weights (Rast) of 382, 363 and 372 respectively, and from analyses are found to be isomeric and were first assigned[2b] the molecular formula, $C_{22}H_{28}O_5$ (or $C_{21}H_{26}O_5$). This molecular formula necessitated the assumption that during alkaline degradation, a C_4 (or C_5) unit had split off from nimbin in addition to the hydrolysis of the two carbomethoxy and the acetoxy groups. Repeated attempts to isolate this small unit proved abortive, and it was found necessary to recheck the molecular formula of these esters by other methods some of which were unsuccessful. Ester B on treatment with methanolic potassium hydrogen carbonate, yields Acid B, m.p. 213–214°, with equivalent weight (420) and molecular formula $C_{24}H_{30}O_6$. On esterification this acid gives Ester B, with molecular formula, $C_{25}H_{32}O_6$. Hence the isomeric (see below) Ester A and Ester C have the same formula.

The difference between nimbic acid and Acid B is a molecule of carbon dioxide. It is evident then that during alkaline degradation, nimbin first forms nimbic acid which is decarboxylated by the action of hot alkali to give Acid B and its isomers. Nimbic acid on treatment with hot methanolic alkali gives a mixture of acids which on esterification and chromatography yields Esters B and C. Ester C on treatment with methanolic potassium hydrogen carbonate gives an amorphous acid m.p. 180–203°, which cannot be crystallized but which on esterification yields Ester C.

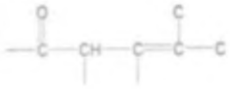
In the infra-red spectra Ester A shows peaks at 3510 (hydroxyl), 1735 (saturated ester), 1715 (saturated ketone) and 1505 and 875 cm^{-1} (furan). This fact coupled with the ultra-violet absorption spectra (maxima at 207 mμ and 297 mμ) indicates that the ketonic carbonyl group is no longer conjugated in Ester A. Ester B shows infra-red peaks at 3600 (hydroxyl), 1740 (saturated ester), 1690 ($\alpha\beta$-unsaturated ketone) and 1505 and 875 cm^{-1} (furan) and ultra-violet absorption maxima at 212 mμ and 327 mμ. Finally, Ester C shows infra-red peaks at 3520 (hydroxyl), 1735 (saturated ester), 1678 ($\alpha\beta$-unsaturated ketone) and 1502 and 875 cm^{-1} (furan) and ultra-violet absorption maxima at 214 mμ and 327 mμ.

In order to settle the interrelation of these three esters, each was treated with hot methanolic potassium hydroxide. In each case after esterification and chromatography, almost equal amounts of Esters B and C were isolated. Thus Esters B and C have an $\alpha\beta$-unsaturated ketonic system and are epimeric at the carbon atom γ to the ketone, from where the carboxylic group of nimbic acid is split off. Ester A in which the ethylenic linkage is no longer conjugated to the ketone, is evidently the $\beta\gamma$-unsaturated isomer of Esters B and C. These reactions can be explained if nimbin has the partial structure I, which on hydrolysis first gives nimbic acid (II). The latter is decarboxylated yielding as shown Ester A (III) and Esters B and C (IV, epimeric at the carbon atom marked with asterisk).

Ester B on catalytic hydrogenation yields dihydro-Ester B, $C_{25}H_{34}O_6$, m.p.

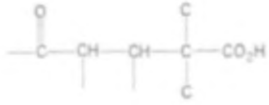
I

II



III

IV



V

VI

137–139°, $[\alpha]_D$ +176° having infra-red peaks at 3580(hydroxyl), 1728(saturated ester), 1702 (saturated ketone) and 1500 and 878 cm^{-1} (furan). Similarly Ester C on hydrogenation gives dihydro-Ester C, $C_{25}H_{34}O_6$, m.p. 150–151°, $[\alpha]_D$ +197° having infra-red peaks at 3550 (hydroxyl), 1728 (saturated ester), 1700 (saturated ketone) and 1500 and 874 cm^{-1} (furan). These two dihydroesters in which the ethylenic linkage conjugated to the ketonic carbonyl has been hydrogenated, can not be epimerized. This fact proves that epimerization only takes place at the carbon atom marked with asterisk in the partial structure IV.

Dihydronimbin on similar treatment with methanolic alkali gives only one dihydroacid, $C_{25}H_{32}O_8$, m.p. 192–195°d, $[\alpha]_D$ +229° in which both the carboxylic groups are retained. This dihydroacid has the partial structure V. On esterification this acid gives desacetyl dihydronimbin, $C_{27}H_{36}O_8$, m.p. 146–147° which on acetylation gives dihydronimbin.

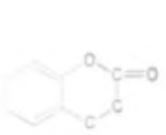
The infra-red spectra of dihydro-Esters B and C (peaks around 1700 cm^{-1}) suggest that the ketonic group of nimbin is in a six membered ring. The partial structure of nimbin can now be enlarged to structure VI. This partial structure, however, needs clarification on an important point. Desacetyl nimbin has two ester peaks at 1730 and 1715 cm^{-1} in the infra-red spectra. The former peak is undoubtedly due to a saturated carbomethoxy group, but the latter peak, which disappears after decarboxylation, has been attributed to an $\alpha\beta$-unsaturated carbomethoxy group by Narasimhan.[8] This fact cannot explain the facile decarboxylation with methanolic base. The latter peak (1715 cm^{-1}) is therefore also due to a saturated carbomethoxy group, which is vinylogously situated with respect to the $\alpha\beta$-unsaturated ketonic carbonyl system. Since on decarboxylation an epimeric centre is formed, the carbon atom α to the carbomethoxy group in nimbin does not contain any hydrogen atom (Structure VI). It was shown by Cole and Thornton[12] that in triterpenoids the saturated carbomethoxy peak in the infra-red appears in the region 1714 to 1725 cm^{-1}.

[12] A. R. H. Cole and D. W. Thornton, *J. Chem. Soc.* 1007 (1956).

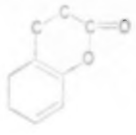
That Esters A, B and C still retain the original carbocyclic ring system is proved by the dehydrogenation of the lithium aluminium hydride reduction product of a mixture of these three esters. The naphthalene derivative isolated from the dehydrogenation was identified as 1,2,5-trimethylnaphthalene.

The reactions of the hydroxyl group in Ester B proved to be secondary in nature. Ester B on acetylation gives a monoacetate, $C_{27}H_{34}O_7$, m.p. 174–175°. On chromium trioxide oxidation by Sarett's method,[14] Ester B gives a diketoester, $C_{25}H_{30}O_6$, m.p. 177°, which does not have any hydroxyl peak in the infra-red, but has peaks at 1710 (saturated ketone and ester), 1680 ($\alpha\beta$-unsaturated ketone) and 1500 and 875 cm^{-1} (furan). The ultra-violet absorption spectra of this diketoester show maxima at 206 and 309 mμ. Desacetyl dihydronimbin also on similar oxidation with chromium trioxide[14] gives a diketodiester, $C_{27}H_{34}O_8$, m.p. 155–156°.

Narasimhan suggested that 'pyronimbic acid', which is formed from nimbic acid and whose infra-red spectra indicate the absence of the ketonic peak at 1687 cm^{-1} has the structure VII or VIII. On repeating the work of Narasimhan, the same enol-lactone was isolated and assigned the molecular formula, $C_{24}H_{28}O_5$. This enol-lactone shows maxima in the ultra-violet at 207 and 278 mμ. It dissolves in methanolic



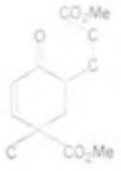
VII



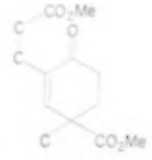
VIII

IX a

IX b



X



XI

potassium hydroxide solution and on acidification yields a mixture of acids, which on esterification followed by chromatography furnish Esters B and C. Individually Acids B and C were subjected to sublimation in vacuum and in each case 'pyronimbic acid' was isolated and identified. It is thus evident that in 'pyronimbic acid' the asymmetry of the epimeric centre marked with asterisk in the partial structure IV has been destroyed. Since the ketone takes part in the enol-lactone formation, the partial

[14] G. I. Poos, W. F. Johns and L. H. Sarett, *J. Amer. Chem. Soc.* 77, 1026 (1955).

structure of 'pyronimbic acid' is either IXa or IXb and not of the types suggested by Narasimhan. These experiments also establish that nimbin has either the partial structure X or XI.

EXPERIMENTAL

The pet ether b.p. 60–80° was used throughout the investigation. The ultra-violet absorption spectra of all the compounds were studied in 95% ethyl alcohol.

Isolation of nimbin

Dried and powdered trunk bark of *M. azadirachta* Linn. (3·6 Kg) was extracted in a Soxhlet with benzene for 20 hr. The residue from the benzene extract was taken up in ether, washed (5% NaOH, and water) and dried (Na_2SO_4). The gummy material (35 g) was partitioned between pet ether and 80% aqueous methanol. The residue (16·8 g) from the methanol layer was acetylated with pyridine (30 cc) and acetic anhydride (30 cc). The crude product (16 g) was chromatographed over alumina (200 g, deactivated with 8 cc of 10% aqueous acetic acid). The crystalline material (4·6 g) eluted with a mixture of pet ether and benzene (1:1) on crystallization from methanol afforded nimbin (2·8 g), m.p. 204–205°, $[\alpha]_D$ +168° ($CHCl_3$). (Reported[7] m.p. 205°, $[\alpha]_D$ +170°.) (Found: C, 65·95; H, 6·79. OCH_3, 11·75. $C.CH_3$, 9·33. $C_{29}H_{36}O_9$ requires: C, 65·98; H, 6·87. OCH_3 (two), 11·7. $C\text{-}CH_3$ (two), 10·19%).

Mol. wt., Found (Rast), 530. Calc., 528.

U.V. λ_{max} 210 mμ (E 32,700) and 330 mμ (E 66).

I.R. ($CHCl_3$) Peaks at 1730 (ester), 1687 (α,β-unsaturated ketone) and 1510 and 875 cm^{-1} (β-substituted furan).

(Nujol) Peaks at 1732 (ester), 1700 (α,β-unsaturated ketone), 1246 (acetate) and 1510 and 875 cm^{-1} (β-substituted furan).

Dihydronimbin

A solution of nimbin (0.5 g) in ethyl acetate (20 cc) was stirred in an atmosphere of hydrogen in presence of 10% palladium charcoal catalyst (0·1 g) until one mole equivalent of hydrogen was absorbed. The solid material (0·48 g), m.p. 208–210° isolated on crystallization from methanol gave dihydronimbin (0·4 g), m.p. 215–216° (reported[8] m.p. 218°), $[\alpha]_D$ +167·5° ($CHCl_3$). (Found: C, 65·70; H, 7·30. $C_{29}H_{38}O_9$ requires: C, 65·64; H, 7·22%)

U.V. λ_{max} 210 mμ (E 16,200) and 298 mμ (E 29)

I.R. ($CHCl_3$) Peaks at 1740 (carbonyl), 1245 (acetate) and 1500 and 872 cm^{-1} (β-substituted furan).

Isolation of acetic acid (as p-bromophenacyl ester) from the alkaline hydrolysis of nimbin

A solution of nimbin (4·67 g) in 5% methanolic potassium hydroxide (200 cc) was refluxed for 2 hr, and acidified with dil HCl and the precipitated solid filtered. The filtrate was adjusted to pH 8, concentrated to a small volume, filtered, acidified with dil H_2SO_4 and extracted with ether. The residual gummy acid mixture (1·3 g) was dissolved in ethyl alcohol (10 cc) and adjusted to pH 7·5 with dil NaOH. The solution was refluxed for 2 hr after the addition of a solution of *p*-bromophenacyl bromide (1·5 g) in ethyl alcohol (20 cc). A gummy residue was chromatographed over alumina (150 g, deactivated with 6 cc of 10% aqueous acetic acid). A mixture of pet ether and benzene (4:1) eluted a solid (0·44 g), m.p. 76–82°, which on crystallization from ethyl alcohol melted at 83–84°. Its mixed m.p. with an authentic specimen of *p*-bromophenacyl ester of acetic acid showed no depression.

Hydrolysis of nimbin with methanolic potassium hydrogen carbonate

Nimbinic acid. A mixture of nimbin (1 g), methanol (20 cc), potassium hydrogen carbonate (1·33 g) and water (6·6 cc) was refluxed for 1½ hr, diluted with water and extracted with ether. The alkaline aqueous layer was acidified with cold dil HCl and the precipitated solid extracted with ether, washed with water and dried (Na_2SO_4). On concentration to a small volume, a solid (0·24 g), m.p. 245–250° crystallized out, and recrystallization from ether gave nimbinic acid, m.p. 259–261°d, $[\alpha]_D$ +112° ($CHCl_3$). (Reported[7] m.p. 263°, $[\alpha]_D$ +129·5°). (Found: C, 65·58; H, 6·85. $C_{28}H_{32}O_8$ requires: C, 66·08; H, 6·83%). Mol. wt., Found (titration at 0°), 456, Calc., 472.

U.V. λ_{max} 208 mμ (E 24,400) and 330 mμ (E 70).

I.R. ($CHCl_3$) Peaks at 3420 (hydroxyl), 1743, 1718 and 1677 (carbonyl) and 1505 and 875 cm^{-1} (β-substituted furan).

Esterification of nimbinic acid

Desacetylnimbin. Nimbinic acid (100 mg) in a mixture of ether and methanol was esterified with an ethereal solution of diazomethane (from 100 mg of nitrosomethyl urea). The ester (90 mg), m.p. 207–210° on crystallization from methanol gave *desacetylnimbin*, m.p. 215–216° (reported[7] m.p. 210–214°), $[\alpha]_D$ +105° ($CHCl_3$). (Found: C, 67·10; H, 6·90. $C_{27}H_{34}O_8$ requires: C, 66·65; H, 7·04%).

I.R. ($CHCl_3$) Peaks at 3420 (hydroxyl), 1730, 1715 (ester), 1680 ($\alpha\beta$-unsaturated ketone) and 1505 and 875 cm^{-1} (β-substituted furan).

Acetylation of desacetylnimbin

Nimbin. Desacetylnimbin (130 mg) was acetylated with pyridine (1·3 cc) and acetic anhydride (1·3 cc) and the crude product (120 mg) on crystallization from methanol gave *nimbin*, m.p. and mixed m.p. 204–205°.

Hydrolysis of nimbin with cold methanolic potassium hydroxide

Nimbic acid. Nimbic acid was prepared from nimbin (2 g) by treatment with cold methanolic potassium hydroxide solution[12]. The crude acid, m.p. 150–151°d, on crystallization from aqueous methanol melted at 159–160°, but after drying melted at 184–185°d, $[\alpha]_D$ +157° (pyridine). (Found: C, 65·12; H, 6·78. $C_{25}H_{30}O_8$ requires: C, 65·49; H, 6·60%).

U.V. λ_{max} 209 mμ (E 14,300) and 327 mμ (E 50).

I.R. (Nujol) Peaks at 3500 (hydroxyl), 1718 (carboxyl), 1680 ($\alpha\beta$-unsaturated ketone) and 1500 and 872 cm^{-1} (β-substituted furan).

Esterification of nimbic acid

Desacetylnimbin. Nimbic acid on esterification gave methyl nimbate, m.p. 212–214°, which was identical with desacetylnimbin (mixed m.p. and infra-red) prepared from nimbinic acid.

Lithium aluminium hydride reduction of nimbin and dehydrogenation of the product

To a cold suspension of lithium aluminium hydride (1·2 g) in dry ether (150 cc) was added a solution of nimbin (1 g) in tetrahydrofuran (20 cc) and dry ether (50 cc). The reaction mixture was kept in the ice bath for 20 min, then refluxed for 5 hr, and treated with water. The precipitated aluminium oxide was filtered and washed with hot chloroform. The combined filtrates were dried (Na_2SO_4) and evaporated to a gummy residue (1·6 g, λ_{max} 206 mμ), which did not crystallize even after acetylation and chromatography.

The gummy reduction product (1 g) was heated with selenium powder (3 g) at 320–340° for 20 hr, and the product ether extracted. The ether solution was washed (10% NaOH and water), dried (Na_2SO_4) and evaporated to give a gummy residue (0·2 g), which was chromatographed over alumina (10 g). The colourless oil (0·07 g) eluted with pet ether was dissolved in methanol and treated with a solution of 1,3,5-trinitrobenzene (0·07 g) in methanol. The product (0·02 g), m.p. 145–148°, on recrystallization from methanol gave orange–red crystals, m.p. 152–154° identical by mixed m.p. with the adduct of 1,3,5-trinitrobenzene and 1,2,5-trimethylnaphthalene. (Found: C, 59·60; H, 4·72. Calc. for $C_{19}H_{17}O_6N_3$: C, 59·53; H, 4·47%).

1,2,5-Trimethylnaphthalene regenerated from the above adduct by passage through a column of alumina with pet ether, had the ultra-violet absorption maxima at 230 mμ (log E 4·86), 278 mμ (log E 3·69), 288 mμ (log E 3·80), 324 mμ (log E 2·85) and 355 mμ (log E 1·22).

Preparation of esters A, B *and* C

Nimbin (2 g) in 5% methanolic potassium hydroxide solution (100 cc) was refluxed for 1 hr, poured into water and extracted with ether. The alkaline aqueous solution was acidified with cold dil HCl, with separation of yellowish white solids. The crude mixture melted over a range (90–140°) and could not be purified by crystallization.

A suspension of the crude mixture of acids in ether was treated with an ethereal solution of

diazomethane (from 1 g of nitrosomethylurea) and kept overnight at room temp. The gummy mixture of esters (1·43 g) was chromatographed over alumina (100 g, deactivated with 4 cc of 10% aqueous acetic acid) and esters A, B and C isolated as follows.

Ester A. The crystalline material eluted with pet ether and benzene (3:2), on crystallization from pet ether and ether afforded Ester A (0·07 g), m.p. 138–139°, $[\alpha]_D$ +130° ($CHCl_3$). (Found: C, 70·47; H, 7·44. $C_{25}H_{32}O_6$ requires: C, 70·07; H, 7·53%). Mol. wt., Found (Rast), 382. Calc., 428.

U.V. λ_{max} 207 mμ (E 13,800) and 297 mμ (E 87).

I.R. ($CHCl_3$) Peaks at 3510 (hydroxyl), 1735 (ester), 1714 (saturated ketone) and 1505 and 875 cm^{-1} (furan).

Ester B. The crystalline material eluted with pet ether and benzene (2:3), on crystallization from pet ether and ether afforded Ester B (0·26 g), m.p. 153–154°, $[\alpha]_D$ +140° ($CHCl_3$). (Found: C, 70·45; H, 7·43. $C_{25}H_{32}O_6$ requires: C, 70·07; H, 7·53%). Mol. wt., Found (Rast), 363. Calc., 428.

U.V. λ_{max} 212 mμ (E 14,300) and 327 mμ (E 67).

I.R. ($CHCl_3$) Peaks at 3600 (hydroxyl), 1740 (ester), 1690 ($\alpha\beta$-unsaturated ketone) and 1505 and 875 cm^{-1} (furan).

Ester C. The crystalline material eluted with benzene, on crystallization from pet ether and ether afforded Ester C (0·28 g), m.p. 158–160°, $[\alpha]_D$ +302° ($CHCl_3$). (Found: C, 70·55; H, 7·50. $C_{25}H_{32}O_6$ requires: C, 70·07; H, 7·53%). Mol. wt., Found (Rast), 372. Calc., 428.

U.V. λ_{max} 214 mμ (E 12,500) and 327 mμ (E 59).

I.R. ($CHCl_3$) Peaks at 3520 (hydroxyl), 1735 (ester), 1678 ($\alpha\beta$-unsaturated ketone) and 1502 and 875 cm^{-1} (furan).

Preparation of the monoacetate of ester B

A solution of Ester B (140 mg) in pyridine (1·4 cc) and acetic anhydride (1·4 cc) was allowed to stand overnight at room temp. The acetate m.p. 165–170° on crystallization from methanol afforded the monoacetate of Ester B (45 mg), m.p. 174–175°, $[\alpha]_D$ +205° ($CHCl_3$). (Found: C, 69·54; H, 7·30. $C_{27}H_{34}O_7$ requires: C, 68·92; H, 7·28%).

Hydrolysis of ester B *with potassium hydrogen carbonate*

Acid B. A mixture of Ester B (130 mg), potassium hydrogen carbonate (130 mg), water (1 cc) and methanol (2 cc) was refluxed for 2 hr, and extracted with ether. The aqueous alkaline solution was acidified with cold dil HCl, yielding material, m.p. 200–209° which on crystallization from dry ether gave Acid B (35 mg), m.p. 213–214°, $[\alpha]_D$ +139° ($CHCl_3$). (Found: C, 69·96; H, 7·49. $C_{24}H_{30}O_6$ requires: C, 69·54; H, 7·30%). Equiv. wt., Found (titration), 420. Calc., 414.

Esterification of acid B

Ester B. Acid B (200 mg) was esterified with an ethereal solution of diazomethane (from 200 mg of nitrosomethylurea). The crude ester (190 mg), m.p. 145–148°, on crystallization from pet ether and ether afforded Ester B, m.p. and mixed m.p. 153–154°.

Hydrolysis of ester C *with potassium hydrogen carbonate*

Amorphous acid C. A mixture of Ester C (280 mg), methanol (7·5 cc), potassium hydrogen carbonate (350 mg) and water (2·5 cc) was refluxed for 2 hr, and extracted with ether. The aqueous alkaline solution on acidification with cold dil HCl afforded amorphous Acid C (190 mg), m.p. 180–203°. All attempts at the crystallization of the solid failed.

Esterification of amphorous acid C

Ester C. Acid C (190 mg) was esterified with an ethereal solution of diazomethane (from 190 mg of nitrosomethylurea) yielding Ester C (100 mg), m.p. and mixed m.p. 158–160°.

Isomerization of ester A *to esters* B *and* C

A solution of Ester A (85 mg) in 5% methanolic potassium hydroxide solution (5 cc) was refluxed for 1 hr, then acidified with cold dil HCl, yielding material, m.p. 140–165°d. This was esterified with ethereal diazomethane (from 85 mg of nitrosomethylurea) and the ester (80 mg) chromatographed over alumina (10 g, deactivated with 0·6 cc of 10% aqueous acetic acid). The solid material,

m.p. 141–145° eluted with pet ether and benzene (3:2), crystallized from pet ether and ether as Ester B (21 mg), m.p. and mixed m.p. 151–153°. The second material eluted with benzene on crystallization from pet ether and ether afforded Ester C (20 mg), m.p. and mixed m.p. 158–160°.

Equilibration of ester B

Similarly Ester B (95 mg) with 5% methanolic potassium hydroxide solution (5 cc) gave a solid acid mixture, which on esterification and chromatography afforded Ester B (31 mg), m.p. and mixed m.p. 152–154° and Ester C (29 mg), m.p. and mixed m.p. 158–159°.

Equilibration of ester C

Ester C (100 mg) with 5% methanolic potassium hydroxide solution (5 cc) gave a solid acid mixture, which on esterification and chromatography afforded Ester B (38 mg), m.p. and mixed m.p. 152–154° and Ester C (36 mg), m.p. and mixed m.p. 158–160°.

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Treatment of nimbic acid with base

Isolation of esters B *and* C. A solution of nimbic acid (1 g) in 5% methanolic potassium hydroxide solution (150 cc) was refluxed for 1 hr, and acidified with dil HCl, yielding a mixture of acids (0·7 g) which on esterification and chromatography afforded Ester B (0·17 g), m.p. and mixed m.p. 153–154° and Ester C (0·16 g), m.p. and mixed m.p. 158–160°.

Dihydro-ester B

A solution of Ester B (0·53 g) in ethyl acetate (25 cc) was stirred in an atmosphere of hydrogen in presence of 10% palladium charcoal catalyst (0·2 g) until one mole equivalent of hydrogen was absorbed. The product (0·5 g) was chromatographed over alumina (20 g, deactivated with 1·2 cc of 10% aqueous acetic acid). Elution with pet ether and benzene (4:1) gave crystalline solids (0·42 g), which on crystallization from pet ether and ether gave dihydro-Ester B, m.p. 137–139°, $[\alpha]_D$ +176° ($CHCl_3$). (Found: C, 70·12; H, 7·71. $C_{25}H_{34}O_6$ requires: C, 69·74; H, 7·96%).

U.V. λ_{max} 209 mμ (E 13,600) and 292 mμ (E 38).

I.R. ($CHCl_3$) Peaks at 3580 (hydroxyl), 1728 (saturated ester), 1702 (saturated ketone) and 1500 and 878 cm^{-1} (furan).

Dihydro-ester C

Similarly Ester C (0·51 g) in ethyl acetate (30 cc) in an atmosphere of hydrogen and in presence of 10% palladium charcoal catalyst (0·3 g) yielded a product (0·62 g) which was chromatographed over alumina and afforded dihydro-Ester C, m.p. 150–151°, $[\alpha]_D$ +197° ($CHCl_3$). (Found: C, 70·13; H, 7·66. $C_{25}H_{34}O_6$ requires: C, 69·74; H, 7·96%).

U.V. λ_{max} 210 mμ (E 12,100) and 288 mμ (E 62).

I.R. ($CHCl_3$) Peaks at 3550 (hydroxyl), 1728(saturated ester), 1700 (saturated ketone) and 1500 and 874 cm^{-1} (furan).

Attempted equilibration of dihydro-ester B

Dihydro-Ester B (95 mg) was treated with 5% methanolic potassium hydroxide solution (5 cc) and the crude acid on esterification and chromatography afforded unchanged dihydro-Ester B (75 mg), m.p. and mixed m.p. 137–138°.

Attempted equilibration of dihydro-ester C

A similar treatment of dihydro-Ester C (82 mg) with 5% methanolic potassium hydroxide solution (5 cc) gave a crude acid, which on esterification followed by chromatography yielded unchanged dihydro-Ester C (60 mg), m.p. and mixed m.p. 150–151°.

Hydrolysis of dihydronimbin

Dihydroacid $C_{25}H_{32}O_8$. A solution of dihydronimbin (2·7 g) in 5% methanolic potassium hydroxide solution (150 cc) was refluxed for 1 hr, acidified with cold dil HCl, and extracted with ether. The ether solution was washed (water), dried (Na_2SO_4) and concentrated to ca. 50 cc. The solid on recrystallization from a mixture of acetone and hexane afforded the dihydroacid, $C_{25}H_{32}O_8$ (0·9 g),

m.p. 192–195°d, $[\alpha]_D$ +229° (pyridine). (Found: C, 65·34; H, 6·84. $C_{35}H_{42}O_8$ requires: C, 65·20; H, 7·00%). Equiv. wt., Found (titration), 236. Calc., 230.

U.V. λ_{max} 208 mμ (E 10,800) and 292 mμ (E 49).

Desacetyl dihydronimbin

The above dihydroacid (1·6 g) was esterified with diazomethane and the crude ester (1·34 g), m.p. 144–146°, after crystallization from pet ether and ether afforded desacetyl dihydronimbin, m.p. 146–147°, $[\alpha]_D$ +138° ($CHCl_3$). (Found: C, 66·70; H, 7·26. $C_{27}H_{34}O_8$ requires: C, 66·37; H, 7·43%).

U.V. λ_{max} 206 mμ (E 12,000) and 292 mμ (E 67).

I.R. ($CHCl_3$) Peaks at 3200 (hydroxyl), 1710 (saturated ester), 1700 (saturated ketone) and 1500 and 875 cm^{-1} (furan).

Acetylation of desacetyl dihydronimbin

Desacetyl dihydronimbin (0·3 g) was acetylated with pyridine (3 cc) and acetic anahydride (3 cc) and the crude product on crystallization from methanol afforded dihydronimbin, m.p. and mixed m.p. 214–215°. The infra-red spectra of this ester was identical with that of dihydronimbin.

Lithium aluminium hydride reduction of the mixture of esters A, B *and* C *and dehydrogenation of the product*

A solution of a gummy mixture of Esters A, B and C (0·95 g) in dry ether (50 cc) was added to a suspension of lithium aluminium hydride (1 g) in dry ether (150 cc). The reaction mixture was kept at 10° for 15 min, then refluxed for 5 hr, yielding a gummy material (0·86 g). This was heated with selenium powder (2·5 g) at 320–340° for 20 hr, and extracted with ether. The gummy residue (0·13 g) on chromatography over alumina and elution with pet ether gave an oil (0·06 g), the 1, 3, 5-trinitrobenzene adduct of which was found to be identical with that of 1, 2, 5-trimethylnaphthalene reported before.

Oxidation of ester B

Diketoester $C_{35}H_{38}O_6$. To a complex prepared[11] from pyridine (1 cc) and chromium trioxide (100 mg) was added a solution of Ester B (100 mg) in pyridine (1 cc) at 15°. The mixture was allowed to stand at room temp for ½ hr. The gummy product (100 mg) was chromatographed over alumina (10 g, deactivated with 0·6 cc of 10% aqueous acetic acid) and the solid (40 mg) eluted with pet ether and benzene (4:1), after crystallization from pet ether afforded the diketoester, m.p. 177°. (Found: C, 70·65; H, 7·09. $C_{35}H_{38}O_6$ requires: C, 70·40; H, 7·09%).

U.V. λ_{max} 206 mμ (E 14,000) and 309 mμ (E 123).

I.R. ($CHCl_3$) Peaks at 1710 (saturated ketone and ester), 1680 (α,β-unsaturated ketone) and 1500 and 875 cm^{-1} (furan).

Oxidation of desacetyl dihydronimbin

Diketodiester $C_{33}H_{34}O_8$. Desacetyl dihydronimbin (110 mg) in pyridine (1 cc) was similarly treated with a complex of chromium trioxide (100 mg) and pyridine (1 cc) yielding a gummy residue (100 mg) which on chromatography over alumina (12 g, deactivated with 0·4 cc of 10% aqueous acetic acid) and elution with pet ether and benzene (2:3) gave material (50 mg) which crystallized from pet ether and ether affording the diketodiester, m.p. 155–156°. (Found: C, 66·97; H, 6·66. $C_{33}H_{34}O_8$ requires: C, 66·65; H, 7·04%).

U.V. λ_{max} 206 mμ (E 14,800) and 304 mμ (E 104).

I.R. ($CHCl_3$) Peaks at 1735 (ketone and ester), 1500 and 872 cm^{-1} (furan).

'Pyronimbic acid'

'Pyronimbic acid' was prepared by the sublimation of nimbic acid[12] in vacuum, and crystallized from methanol, m.p. 265–267°d (reported[12] m.p. 263–267°), $[\alpha]_D$ +117° ($CHCl_3$). (Found: C, 72·84; H, 6·89. $C_{24}H_{28}O_4$ requires: C, 72·70; H, 7·12%). Mol. wt., Found (Rast), 384, (titration), 380. Calc., 396.

Similarly acids B and C on sublimation followed by crystallization afforded 'pyronimbic acid', m.p. and mixed m.p. 265–267°d.

Conversion of 'pyronimbic acid' to esters B *and* C

'Pyronimbic acid' (125 mg) was allowed to stand for ½ hr with 5% methanolic potassium hydroxide solution (2 cc), and acidified with cold dil HCl. The crude acid, on esterification followed by chromatography afforded Ester B (40 mg), m.p. and mixed m.p. 152–154° and Ester C (35 mg), m.p. and mixed m.p. 158–160°.

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PAPILIONACEOUS ALKALOIDS—XXXVIII

CONTRIBUTION TO THE CHEMISTRY AND STEREOCHEMISTRY OF RETAMINE

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Abstract—Three new bases related to retamine are described: chlororetamine, isoretamine, and chloroisoretamine. Retamine and isoretamine are 8-hydroxy-(+)-sparteine epimers; chlororetamine is an 8-chloro-(+)-sparteine; chloroisoretamine is an 11-chloro-(+)-α-isosparteine. In the transformation of isoretamine to chloroisoretamine the rearrangement is explained by the modern concept of bridge carbonium ion.

In previous papers[1], retamine has been formulated as 7- or 9-hydroxy-(+)-sparteine, the 7 and 9 positions of sparteine (I) being considered as equivalent. Ribas and Fraga[1b] have excluded position 8 for the hydroxyl group in retamine, as a ketone cannot be obtained by oxidation. Having also excluded the 6 and 11 positions owing to the failure of several reactions, the only remaining position for the tertiary hydroxyl group was 7 or 9.

Leonard and Marion *et al.*[2], however proved the structural formula of sparteine to be IIa, with the positions 7 and 9 no longer equivalent, and therefore, an investigation of the problem was undertaken. This work is summarized in the following table.

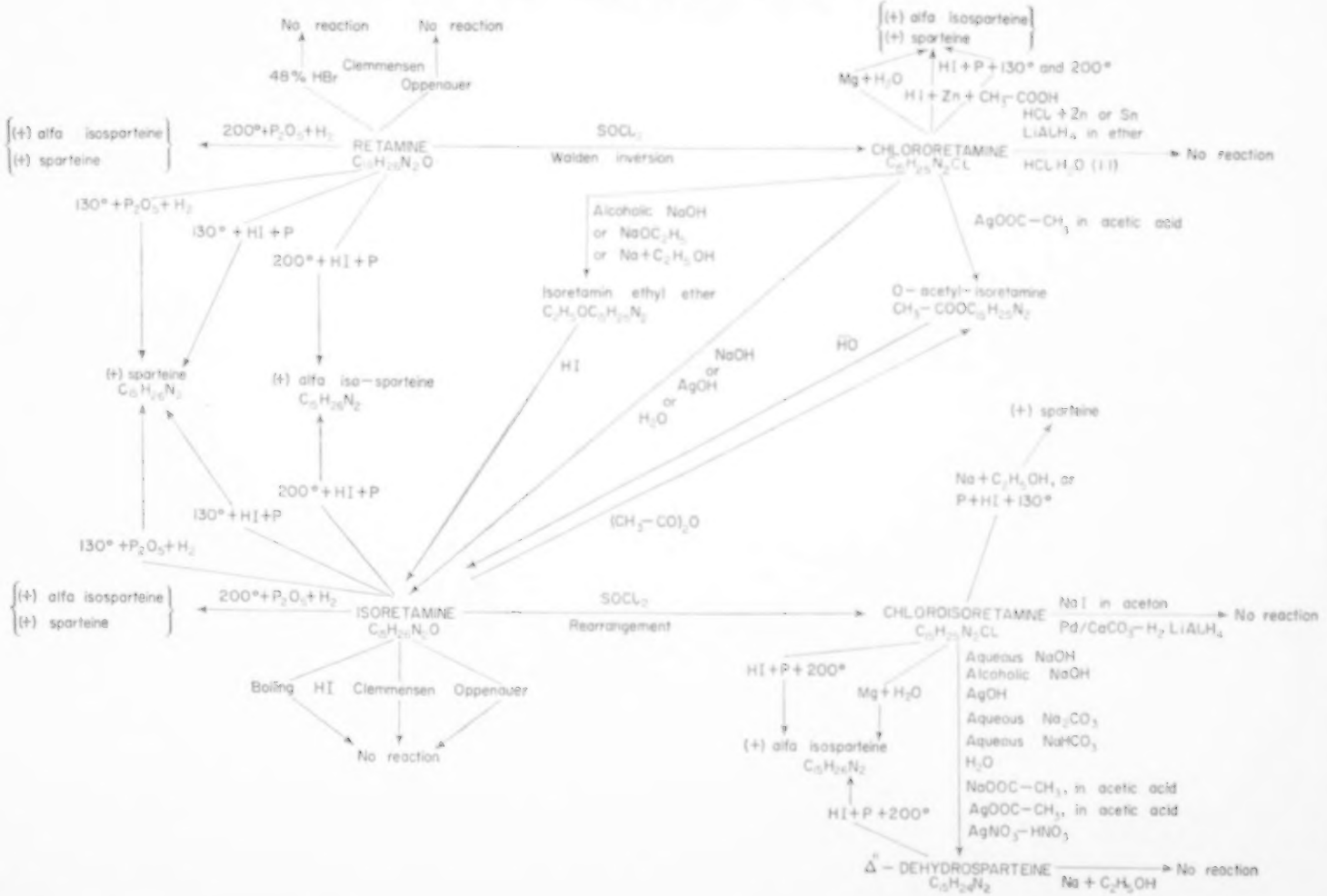
Chlororetamine, a new base, $C_{15}H_{25}N_2Cl$, was obtained by substitution of the hydroxyl group in retamine by chlorine. The carbon–nitrogen skeleton of retamine remains unchanged in this new base, as it can be transformed into a mixture of (+)-α-isosparteine (III) and (+)-sparteine (IIa) by the following methods: reduction with Zn dust and hydrobromic acid in acetic acid, reduction with red phosphorus and hydriodic acid, and hydrolysis of magnesium–chlororetamine formed by treatment of the new base with magnesium in anhydrous ether.

The chlorine atom of the chlororetamine is readily substituted by the action of nucleophilic reagents (NaOH, AgOH, H_2O, etc.) giving rise to a second new base, isoretamine, $C_{15}H_{26}N_2O$, m.p. 162°, an isomer of retamine with the same carbon–nitrogen skeleton since (+)-sparteine and (+)-α-isosparteine are formed by reduction with red phosphorus and hydriodic acid at 130° and 200° respectively.

Both isoretamine and retamine on heating with P_2O_5 at 130° yield a dehydrobase, which can be hydrogenated to (+)-sparteine, and on heating either compound with the same reagent at 200° a mixture of dehydrobases is obtained which on hydrogenation gives (+)-α-isosparteine and (+)-sparteine. The hydroxyl group in retamine or

[1a] I. Ribas, A. Sánchez and E. Primo, *Anales fís. y quím.* **42**, 516 (1946); [b] I. Ribas and F. Fraga, *Anales Real Soc. Españ. Fís. y Quím.* **45B**, 1426 (1949); [c] F. Fraga and I. Ribas, *Ibid.* **46B**, 665 (1950).
[2a] N. J. Leonard and R. E. Beyler, *J. Amer. Chem. Soc.* **72**, 1316 (1950); [b] L. Marion and N. J. Leonard, *Canad. J. Chem.* **29**, 355 (1951); [c] L. Marion, *Bull. Soc. Chim. Fr.* 1193 (1954).

Table summary of retamine chemistry



isoretamine cannot be oxidized to a ketone by the Oppenauer method or with chromic acid.

These reactions showing similar chemical behaviour indicate that retamine and isoretamine are hydroxy-epimer compounds. Neither can be 7- or 9-hydroxy-sparteine as these positions do not allow epimer compounds.

The same conclusion is reached by the examination of the chemical activity of chlororetamine. Substitution of the chlorine by a hydroxyl group quantitatively is independent of the concentration of the nucleophilic reagent and even takes place with water. Therefore, this transformation into isoretamine is a first class nucleophilic substitution reaction (S_N1), which proceeds by a carbonium ion mechanism. But the carbonium ion formation is not consistent with the 7 and 9 positions, which contain bridged head carbons, unable to produce the required structure.[3]

Positions 6 and 11 for the hydroxyl group in the retamine are excluded as 11- (or 6-) hydroxy-sparteine should readily be dehydrated, show a ketone form or be reduced electrolytically, but retamine and isoretamine fail to give these reactions.

Molecular rotations, infra-red spectra, dehydration and the reactions of a new base, chloroisoretamine, indicate 8 as the only position for the hydroxyl group in retamine and isoretamine.

Molecular rotations. If from the molecular rotation (M_D) of retamine, or isoretamine, that of (+)-sparteine is substracted the contribution of the asymmetric centre at C_8 is obtained. The molecular rotation calculated from the value of this contribution is in perfect agreement with the experimental value.

Compound	$[\alpha]_D$	M_D (found)	M_D (calculated)
Retamine	+46·2°	+115	+115
Isoretamine	−14·2°	−35	−35
(+)-Sparteine	+17°	+40	

$$M_D \text{ retamine} - M_D \text{ (+)-sparteine} = 115 - 40 = +75$$
$$M_D \text{ isoretamine} - M_D \text{ (+)-sparteine} = -35 - 40 = -75$$
$$\text{Contribution of the asymmetric centre: } \pm 75$$

Infra-red spectra. Cole *et al.*[4] found that the hydroxyl group of 3-hydroxysteroids exhibits a band between 995 and 1055 cm^{-1}, an axial hydroxyl group absorbing at 995–1035 cm^{-1}, and an equatorial one at 1035–1055 cm^{-1}; the difference being 20–40 cm^{-1}. The infra-red spectra of retamine, isoretamine, and the related (+)-sparteine and (+)-α-isosparteine, under identical conditions (4% in CS_2) show the following intensities:

Retamine	1007 (35%)	1025 (50%)	1050 (50%)		
Isoretamine	1007 (50%)	1027 (55%)	1047 (60%)		
Sparteine	1011 (50%)			1070 (55%)	
α-Isosparteine	1007 (30%)				1107 (30%)

The two bands shown in the spectra of retamine (1025, 1050 cm^{-1}) and isoretamine (1027, 1047 cm^{-1}) must be produced by the hydroxyl group as they do not occur in

[3] D. Bethell and V. Gold, *Quart. Rev.* **12**, 185 (1958).
[4] A. R. H. Cole, R. N. Jones and K. Dobriner, *J. Amer. Chem. Soc.* **74**, 5571 (1952).

the spectra of the related compounds. The frequency, difference and shape of the bands indicate that the lower one is due to an axial, and the higher to an equatorial hydroxyl. But as both retamine and isoretamine have only one hydroxyl group, this must be axial to one ring and equatorial to the other; and this feature can only occur at C_8 position.

The selection of configurations. Formulae IV, IIb and IIc are proposed for retamine isoretamine and chlororetamine respectively. No epimer for chlororetamine is possible since the C_8 position is hindered by the axial C_{12}-hydrogen atom of the D-ring. With Catalin molecular models (Waltham, Essex) it is clearly seen that the voluminous chlorine atom has no room at this hindered position for epimer formation. Isoretamine, obtained from chlororetamine by hydrolysis, must be the less hindered epimer IIb, leaving configuration IV for retamine. A Walden inversion at C_8 must occur in the change of retamine to chlororetamine; but the configuration at C_8 is preserved in going from the chlororetamine to isoretamine. The molecular rotation changes are in good agreement:

$$M_D \text{ retamine} - M_D \text{ (+)-sparteine} = +75$$
$$M_D \text{ chlororetamine} - M_D \text{ (+)-sparteine} = -28{\cdot}4$$
$$M_D \text{ isoretamine} - M_D \text{ (+)-sparteine} = -75$$

The mechanism for these reaction changes is as follows: the action of thionyl chloride on retamine should give rise to chlorosulphite (V), which is possible according to the Catalin molecular models, and the decomposition of this intermediate (V) with simultaneous attack of the chloride ion, from the less hindered side, should bring about the formation of chlororetamine (IIc). Although this compound reacts with nucleophilic reagents by the intermediate of carbonium ion (VI), it always gives isoretamine (IIb) or the corresponding derivative (IId, IIe) because steric hindrance precludes the formation of an epimer.

Chloroisoretamine and its chemical behaviour. Chloroisoretamine, a new base, $C_{15}H_{25}N_2$ Cl, m.p. 90°, isomeric with chlororetamine and with the same carbon–nitrogen skeleton, is obtained from isoretamine dihydrochloride on treatment with thionyl chloride. It reacts with nucleophilic reagents to give Δ^{11}-dehydrosparteine (VII), whose structure has been established.[5] As chlororetamine under the same conditions undergoes a substitution, this reaction establishes the chlorine atom at C_{11} in chloroisoretamine.

There are two possible configurations for 11-chlorosparteine represented by VIII and IX. Formula VIII is preferred as the chlorine atom is *axial* respecting to both rings C and D and is *trans* with regard to the fourth N_{16} valency, and therefore the four centres participating in the reaction are in the same plain. This structure is supported by the fact that chloroisoretamine readily undergoes elimination reactions, $\Delta^{11,16}$-dehydrosparteinium (X) hydrochloride being produced by heating chloroisoretamine with water on a steam bath. Moreover, its infra-red spectrum shows bands at 800 cm^{-1} and 3457 cm^{-1}, which are typical of the α-isosparteine conformation to which VIII belongs. The fact that chloroisoretamine is a crystalline solid, like α-isosparteine, and not a liquid like chlororetamine and sparteine, is in agreement with the same statement.

[5] N. J. Leonard, P. D. Thomas and V. W. Gash, *J. Amer. Chem. Soc.* 77, 1552 (1955).

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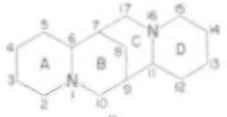
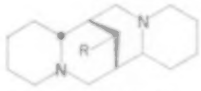
In the formation of chloroisoretamine the action of thionyl chloride on isoretamine should give the chlorosulphite (XI); but the steric hindrance of the epimer position of this intermediate forbids the chloride ion attack at C_8. This attack must then take place at C_{11}, with the migration of a hydrogen from C_{11} to C_8, the elimination of SO_2Cl, and the formation of chloroisoretamine.

The intermediate formation of a bridged carbon–hydrogen ion between C_8–C_{11}, usual in policyclic bridged compounds,[6] may facilitate the 1:3-interaction between C_{11}–C_8. Furthermore, the reaction causes a Walden inversion at C_{11}, so that the chloroisoretamine is the 11-chloro-(+)-α-isosparteine (or 6-chloro-(+)-α-isosparteine, VIII).

Dehydration and other reactions common to retamine and isoretamine. An explanation of these reactions is only possible if the hydroxyl group is located at C_8. Both 8-hydroxysparteines are unable to form a double bond between C_7–C_8 or C_8–C_9 by the elimination of one molecule of water, as the formation of these double bonds requires a valency plain structure at C_7 or C_9, prevented by the rigid tetrahedric

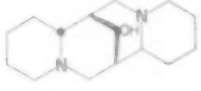


I

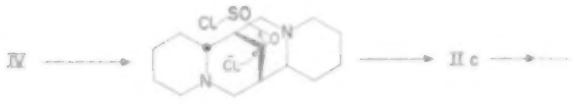


II a: R=H II d: R=CH_3COO
II b: R=HO II e: R=C_2H_5O
II c: R=Cl II f: R=C_6H_5COO

III



IV



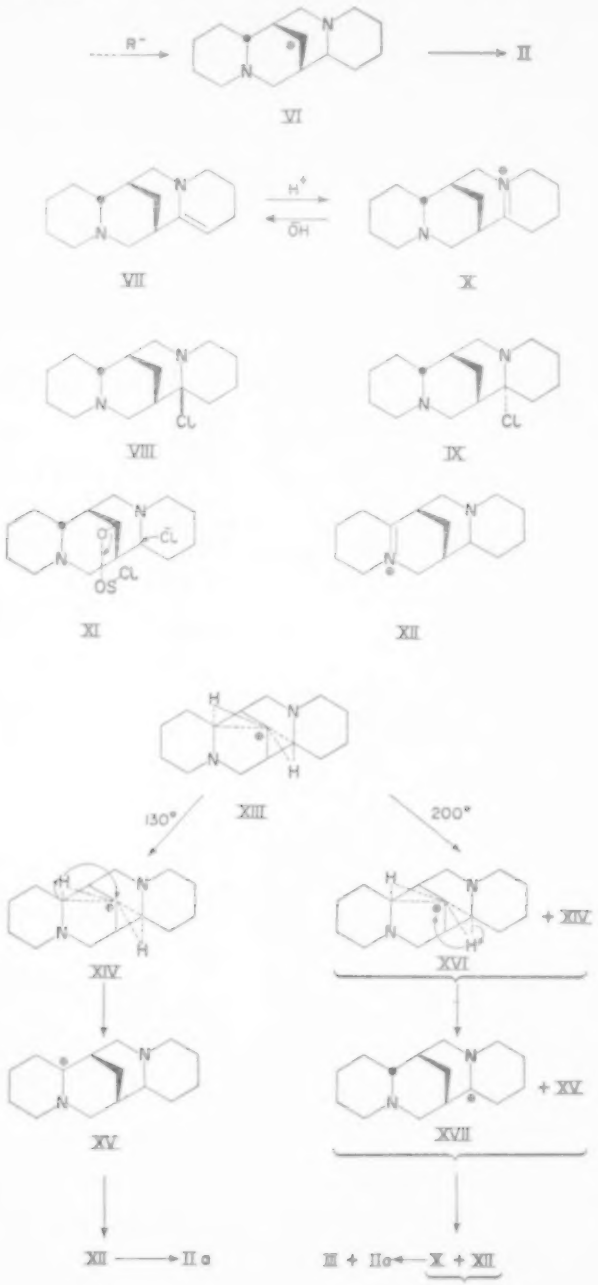
V

structures produced by the convergence of three hexagonal rings (bridgehead carbons). The 8-hydroxysparteines are, therefore, not easy dehydrated; but under vigorous conditions a carbonium ion at C_8 may be formed. This spreads a bridge between the carbons and hydrogens of the 6 and 11 positions (XIII) giving rise to a bridged carbon–hydrogen ion. At low temperature, this bridged ion should react by picking up the twice axial hydrogen at C_6 (XIV) and donating to this position the whole positive charge, with the formation of the classical ion XV. At high temperature, the bridged ion reacts at C_{11} (XVI), in the same way, giving the carbonium ion XVII. Both classical carbonium ions XV and XVII will be converted in the usual way into the enamonium salts XII and X, which on hydrogenation yield (+)-sparteine (IIa) and (+)-α-isosparteine (III) respectively.

The retamine and isoretamine reductions with red phosphorus and hydriodic

[6] [a] T. P. Nevell, E. de Salas and C. L. Wilson, *J. Chem. Soc.* 1188 (1939); [b] J. D. Roberts, C. C. Lee and W. H. Saunders, *J. Amer. Chem. Soc.* **76**, 4501 (1954); [c] S. Winstein and M. Shatavsky, *Chem. & Ind.* 56 (1956); [d] A. Gagneux and C. A. Grob, *Helv. Chim. Acta* **42**, 1753 (1959).

acid, producing at 130° (+)-sparteine and at 200° (+)-α-isosparteine, are similarly explained by bridged hydrogen–carbonium ion formation. In the first case the bridged ion operates at C_6 and the reduction product is (+)-sparteine, and in the second case at C_{11}, producing (+)-α-isosparteine on reduction.



EXPERIMENTAL

Melting points are uncorrected. Unless specified to the contrary, the reaction products were isolated by ether extraction from an aqueous solution, made alkaline with sodium hydroxide or ammonia. The ether extracts were dried with sodium sulphate (or potassium carbonate) and evaporated on a steam bath.

The chromatography, on Whatman No. 1 paper, was performed according to conditions by Munier[7]. Sparteine and α-isosparteine however, always gave the same spots under these conditions, but they could be separated on Whatman No. 1 paper salted with a buffered solution of citric acid (0·1 M; 11·18 ml)–disodium phosphate (0·2 M; 8·82 ml), or citric acid (0·2 N; 100 ml)–sodium citrate (50 ml 0·2 N NaOH) at pH 4·4 in both cases and developed with n-butanol–water (Sparteine $R_f = 0{\cdot}22$; α-isosparteine $R_f = 0{\cdot}33$).

Retamine (IV). The retamine, m.p. 166°, was isolated from *Retama sphaerocarpa Boiss.*,[7a] and recrystallized from ethanol. $[\alpha]_D^{20}$ +46·2° (*c* 1·017; absolute ethanol).

Chlororetamine (IIc).

Retamine (1·0 g) dissolved in conc HCl (1·2 ml) was converted to the dihydrochloride by removal of water (*in vacuo* on a steam bath). Thionyl chloride (1·3 ml) was added, and the solution heated at 85–90° for 50 min. After addition of ice-water, the base, an oil (1·05 g) was converted into the following salts:

(a) The *monoperchlorate* crystallized from methanol had m.p. 243–244° dec. (Found: C, 48·9; H, 7·1; N, 7·9; Cl, 19·1. $C_{15}H_{25}N_2Cl{\cdot}ClO_4H$ requires: C, 48·8; H, 7·1; N, 7·6; Cl, 19·0%).

(b) *Chlororetamine monochlorozincate*. To chlororetamine (0·22 g of the oil) dissolved in ethanol (0·5 ml) 3 N chlorozincic acid (0·25 ml) was added, yielding white crystals of chlororetamine monochlorozincate (0·31 g) m.p. 318–320° dec. (Found: Cl, 29·6; $C_{15}H_{25}N_2Cl{\cdot}Cl_4ZnH_2$ requires: Cl, 29·7%).

(c) *Chlororetamine dipicrate*. This was obtained by mixing an aqueous solution of chlororetamine monochlorozincate with saturated solution of picric acid, and had m.p. 208° dec. from ethanol. (Found: C, 45·9; H, 4·4. $C_{15}H_{25}N_2Cl{\cdot}2C_6H_3N_3O_7$ requires: C, 44·6; H, 4·3%).

Chlororetamine. This was obtained, in the usual way, from monoperchlorate as a colourless oil, with a strong basic reaction. $[\alpha]_D^{21}$ +4·3° (*c* 2·3; absolute ethanol).

Isoretamine (IIb).

Chlororetamine (1·06 g) was converted into its monochlorozincate (1·4 g) and heated with water (50 ml) on a steam bath for 45 min. The isoretamine (0·85 g) recrystallized from acetone m.p. 162°; sublimation point 120–125°/0·05 mm $[\alpha]_D^{21}$ −14·2° (*c* 1·02%; absolute ethanol). (Found: C, 71·9; H, 10·65; N, 10·9. M. wt. by Rast, 236. $C_{15}H_{26}N_2O$ requires: C, 71·9; H, 10·5; N, 11·2%. M. wt. 250).

(a) *Isoretamine monoperchlorate*. Crystallized from methanol, m.p. 195°. (Found: C, 51·6; H, 7·7; N, 23·0. $C_{15}H_{26}N_2O{\cdot}ClO_4H$ requires: C, 51·4; H, 7·7; N, 22·8%).

(b) *Isoretamine diperchlorate*. To the base dissolved in methanol, 70% solution of perchloric acid was added till Congo red changed to blue. The product crystallized from methanol, m.p. of the anhydrous salt 230–232° dec. (Found: C, 39·5; H, 6·1. $C_{15}H_{26}N_2O{\cdot}2ClO_4H$ requires: C, 39·9; H, 6·25%).

(c) *Isoretamine dipicrate* crystallized from ethanol as bright yellow needles, m.p. 195°. (Found: C, 45·75; H, 4·6. $C_{15}H_{26}N_2O{\cdot}2C_6H_3N_3O_7$ requires: C, 45·76; H, 4·6%).

(d) *Isoretamine monohydriodide*. Isoretamine (0·52 g) in warm absolute ethanol (2·5 ml) was treated with 3·0 ml hydriodic acid (sp. gr. = 1·7) and the product (0·44 g) crystallized from methanol, m.p. 246°. (Found: I, 33·7. $C_{15}H_{26}N_2O{\cdot}HI$ requires I, 33·5%).

(e) *Isoretamine chloromercuriate*. To isoretamine (0·3 g) in ethanol conc HCl (0·25 ml) and 5% mercuric chloride was added and the product (0·75 g), crystallized from 10% HCl, had m.p. 250° dec (Found: Hg, 32·85; Cl, 23·2. $C_{15}H_{26}N_2O{\cdot}Cl_4HgH_2{\cdot}H_2O$ requires: Hg, 32·7; Cl, 23·15%).

(f) *Isoretamine monochlorozincate*. Isoretamine (0·27 g) in ethanol (1 ml) was treated with 3 N chlorozincic acid (0·4 ml) and the product (0·51 g), crystallized from water, had m.p. 318° dec (Found: Cl, 29·8; H_2O, 3·78. $C_{15}H_{26}N_2O{\cdot}Cl_4ZnH_2{\cdot}H_2O$ requires: Cl, 29·7; H_2O, 3·77%).

[7a] R. Munier, *Bull. Soc. Chim. Fr.* 852 (1952); [7] R. Munier, *Bull. Soc. Chim. Biol.* **35**, 1225 (1953).

(g) O-*acetyl-isoretamine* (IId) *monoperchlorate*. Isoretamine (0·10 g) was heated with acetic anhydride (1·0 ml) on a steam bath for 30 min, acetic anhydride removed by distillation *in vacuo*, methanol (0·4 ml) and 70% perchloric acid added till neutral. The product crystallized from methanol as rhombic plates, m.p. 206–208°. (Found: C, 51·1; H, 7·1; N, 7·2. $C_{15}H_{22}N_2OCOCH_3 \cdot ClO_4H$ requires: C, 51·9; H, 7·4; N, 7·1%).

(h) O-*benzoyl-isoretamine* (IIf) *dihydrochloride*. Isoretamine (0·18 g) in dry benzene (0·7 ml) was refluxed with benzoyl chloride (0·5 ml) for 2 hr. The benzoyl base, an oil (0·16 g) in ethanol (2·6 ml), was treated with a few drops HCl and ether (20 ml) and the O-benzoyl-isoretamine dihydrochloride crystallized (0·14 g), m.p. 213–215° (anhydrous product). (Found: Cl, 16·2. $C_{15}H_{22}N_2OCOC_6H_5 \cdot 2H$ Cl requires: Cl, 16·6%).

Chloroisoretamine (VIII).

This new base was obtained from isoretamine following the technique for chlororetamine from retamine. Isoretamine dihydrochloride (from isoretamine, 2·0 g, and hydrochloric acid, 2·4 ml), well dried, was heated with thionyl chloride (2·4 ml) at 85–90° for 1 hr. The reaction product crystallized from acetone as white prismatic needles (1·2 g), m.p. 90°; sublimation point 80–85°/0·05 mm; $[\alpha]_D^{22}$ +31·3° (*c* 2·17; absolute ethanol). (Found: C, 66·97; H, 9·5; Cl, 13·0. $C_{15}H_{25}N_2Cl$ requires: C, 67·0; H, 9·3; Cl, 13·2%).

(a) *Chloroisoretamine dipicrate*. Chloroisoretamine (0·05 g) dissolved in the smallest amount ethanol, was treated with saturated ethanolic solution of picric acid till Congo red paper turned blue. The salt (0·09 g) recrystallized from ethanol, m.p. 208–209°. (Found: C, 44·9; H, 4·7. $C_{15}H_{25}N_2$ $Cl \cdot 2C_6H_3N_3O_7$ requires: C, 44·6; H, 4·3%).

(b) *Chloroisoretamine monoperchlorate*. The base in methanol was treated with perchloric acid till just acid, and adjusting the pH with ammonia to 8. By partial evaporation of the solvent, the reaction product crystallized. Recrystallization from methanol–acetone gave colourless prisms m.p. 196–197°. (Found: C, 49·2; H, 6·9. $C_{15}H_{25}N_2Cl \cdot ClO_4H$ requires: C, 48·8; H, 7·1%).

(c) *Chloroisoretamine diperchlorate*. Chloroisoretamine (0·06 g), dissolved in the minimum of methanol, was treated with 20% perchloric acid till acid. The salt was recrystallized from methanol as white needles, m.p. 255–256°. (Found: C, 37·4; H, 5·6. $C_{14}H_{28}N_2Cl \cdot 2ClO_4H$ requires: C, 38·4; H, 5·8%).

Chemical Behaviour of Retamine, Isoretamine and Related Compounds

1. *Negative reactions*

Retamine and isoretamine were recovered unchanged after being submitted to the following reactions: Oppenauer oxidation, silver hydroxide oxidation, Clemmensen reduction, reaction with boiling 57% hydriodic acid (1 hr), and treatment with boiling 48% hydrobromic acid (6 hr).

2. *Dehydrations*

(a) *Retamine dehydration at* 130° *with phosphorus pentoxide*. Retamine (0·5 g) mixed with phosphorus pentoxide (4·5 g) was heated at 130° for 4 hr. After addition of ice, the reaction product, a basic oil (0·26 g), in N hydrochloric acid (25 ml), was hydrogenated over Adams catalyst (0·037 g) for 2 hr. The solution was made alkaline with 33% NaOH and steam distilled. In the distillate (300 ml) the base was precipitated with excess picric acid. The crude picrate (0·27 g) recrystallized from methanol as (+)-sparteine dipicrate (0·12 g), m.p. 205°, identical with an authentic specimen (mixed m.p., infra-red spectrum, and R_f number, AcONa paper. Ba15. $R_f = 0{\cdot}82$).

(b) *Retamine dehydration with phosphorus pentoxide at* 200°. Retamine (0·1 g) and P_4O_{10} (1·0 g) was heated at 200–220° for 6 hr and the product, after hydrogenation, gave a mixture (0·06 g) of 2 bases: one, in larger proportion, was identified as α-isosparteine by R_f number, and the other identified, in the same way, as (+)-sparteine.

(c) *Isoretamine dehydrations with phosphorus pentoxide at* 130° *and* 200°. These two dehydrations under similar conditions gave the same results as retamine, grouped together in Table 1.

3. *Reductions*

(a) *Retamine reduction with hydriodic acid and red phosphorus at* 200°. Retamine (0·1 g), red phosphorus (0·1 g) and hydriodic acid (1 ml; sp. gr. 1·7) were heated in a sealed tube at 200° for 50 hr. The reaction product was a mixture of a crystalline solid (0·04 g) and oil. The solid was

identified as (+)-α-isosparteine by comparison its m.p. 95–115° and R_f number with an authentic sample (NaOAc paper. Ba2. $R_f = 0{\cdot}82$; KCl paper. Bc2. $R_f = 0{\cdot}76$), and m.p. of its dipicrate 219–220° dec. The oil, a complex mixture, on paper chromatography (NaOAc paper. Ba2) showed, at least, four spots: one of them coincided with that of α-isosparteine ($R_f = 0{\cdot}82$) and a second with that of Δ^{11}-dehydrosparteine ($R_f = 0{\cdot}55$).

Table 1. Dehydrations with P_2O_5

Product to be dehydrated	Heating temp. and time	Hydrogenated dehydrobase	Identified
Retamine	130°, 4 hr	(+)-sparteine	as dipicrate
Isoretamine	130°, 4 hr	(+)-sparteine	as dipicrate
Retamine	200°, 6 hr	(+)-α-isosparteine and (+)-sparteine	by its R_f
Isoretamine	200°, 6 hr	(+)-α-isosparteine and (+)-sparteine	by its R_f

Table 2. Reductions with hydriodic acid and red phosphorus

Product to be reduced	Heating temp. and time	Reduction product	Identification
Retamine	200°; 50 hr	(+)-α-isosparteine	M.p.; dipicrate; R_f
Isoretamine	200°; 50 hr	(+)-α-isosparteine	M.p.; dipicrate; diperchlorate; R_f
Retamine	130°; 100 hr	(+)-sparteine	Dipicrate; monoperchlorate; dihydrobromide; bisulphate
Isoretamine	130°; 100 hr	(+)-sparteine	Dipicrate; R_f
Chlororetamine	200°; 50 hr	(+)-α-isosparteine and (+)-sparteine	M.p.; R_f Dipicrate; R_f
Chloroisoretamine	200°; 50 hr	(+)-α-isosparteine	M.p.; dipicrate; R_f
Chlororetamine	130°; 100 hr	(+)-α-isosparteine and (+)-sparteine	R_f R_f
Chloroisoretamine	130°; 100 hr	(+)-sparteine	Dipicrate; R_f

(b) *Isoretamine reduction with boiling hydriodic acid and red phosphorus.* Isoretamine (0·25 g), red phosphorus (0·6 g) and hydriodic acid (6 ml; sp. gr. 1·7) was refluxed for 100 hr. After treatment with zinc dust (0·5 g), the product, an oil (0·28 g), in pet ether (25 ml b.p. 50–70°) was chromatographed on alumina (10 g). Elution with pet ether gave (+) sparteine identified as dipicrate (0·13 g), m.p. 204–205°, by comparison with an authentic specimen.

(c) *Other reductions of related compounds with hydriodic acid and red phosphorus.* Many other reductions were carried out under similar conditions and with similar results, which are grouped together in Table 2.

(d) *Chloroisoretamine reduction through the respective Grignard compound.* Magnesium (0·1 g) in anhydrous ether (8 ml) was treated with bromobenzene (0·47 g). After the reaction had proceeded, chloroisoretamine (0·27 g) was added and the mixture refluxed for 13 hr. The reaction product, hydrolysed by dil HCl, was an oil (0·20 g) from which (+)-α-isosparteine (0·06 g) was isolated and identified by its m.p. 95–110°, picrate m.p. 218° dec, and perchlorate m.p. 264° dec.

(e) *Chlororetamine reduction through the respective Grignard compound.* When the reaction between magnesium (0·14 g) and ethyl bromide (0·38 ml) in anhydrous ether (15 ml) had started,

TABLE 3

Starting compound	Reagent	Reaction conditions	Reaction product
Chlororetamine (0·68 g)	10% NaOH/EtOH	10 days, room temp. or 15 min steam bath	Isoretamine (0·54 g)
Chloroisoretamine (0·25 g)	10% NaOH/EtOH	90 min steam bath	Δ^{11}-Dehydrosparteine (0·21 g diperchlorate)
Chlororetamine (0·10 g)	H_2O (Cu_2Cl_2 trace)	1 hr; steam bath	Isoretamine (0·08 g)
Chloroisoretamine (0·13 g)	H_2O (Cu_2Cl_2 trace)	30 min; steam bath	Δ^{11}-Dehydrosparteine (0·3 g dipicrate)
Chlororetamine (0·22 g monoperchlorate)	AgOAc/AcOH (0·09 g/5 ml)	reflux. 15 min	O-Acetyl-isoretamine (0·16 g monoperchlorate)
Chloroisoretamine (0·16 g)	AgOAc/AcOH (0·08 g/5 ml)	reflux. 15 min	Δ^{11}-Dehydrosparteine (0·15 g diperchlorate)
Chlororetamine (0·10 g)	AgOH/EtOH	4 hr; room temp.	Isoretamine (0·08 g)
Chloroisoretamine (0·10 g)	AgOH/EtOH	45 min; steam bath	Δ^{11}-Dehydrosparteine (0·08 g free base)
Chlororetamine	NaOEt/EtOH	2½ hr; steam bath	Isoretamine ethyl ether (see below)
Chloroisoretamine	NaOEt/EtOH	2 hr; steam bath	Δ^{11}-Dehydrosparteine

chlororetamine (0·2 g) in ether (10 ml) was added and the mixture refluxed for 2 hr. After acidic hydrolysis, the product (0·18 g) in pet ether (40 ml) was chromatographed on alumina (8 g) and the first 8 fractions eluted with the same solvent, gave a colourless oil (0·055 g) which was converted into (+)-sparteine dipicrate, m.p. 204–205°. The last fractions eluted with pet ether/benzene (10/1) gave a solid, which after sublimation (0·01 g) was converted in picrate m.p. 215–216° dec and identified as α-isosparteine dipicrate.

(f) *Chlororetamine reduction with zinc dust and hydrobromic acid in acetic acid.* Chlororetamine (0·25 g), hydrobromic acid (2 ml; sp. gr 1·38), zinc dust (1·5 g) and acetic acid (10 ml) were refluxed for 20 hr. The reaction product, an oil (0·21 g). treated with acetone, gave crystals (0·03 g) of (+)-α-isosparteine. The oil separated from the crystalline solid in pet ether (50 ml; b.p. 50–70°) was chromatographed on alumina (10 g). The 6 first fractions eluted with the same solvent, gave an oil (0·035 g) identified as (+)-sparteine by mixed m.p. of its dipicrate (204°).

(g) *Chloroisoretamine reduction with sodium and ethanol.* Chloroisoretamine (0·25 g) in absolute ethanol (25 ml) was treated with sodium (3 g). The reaction product, steam distilled was precipitated with picric acid. The precipitate (0·52 g), after recrystailization from acetone, was identified as (+)-sparteine dipicrate, m.p. 204–205°. The identification was confirmed by m.p. and mixed m.p. of its perchlorate (170°) with (+)-sparteine monoperchlorate.

(h) *Attempted reduction of chlororetamine with sodium and ethanol.* Chlororetamine (0·56 g) in anhydrous ethanol (50 ml) was treated with sodium (6 g). The product worked up as in the foregoing preparation gave only an impure picrate. The base (0·32 g) from the crude picrate (0·90 g) in methanol, was treated with 20% perchloric acid till acid. The reaction product, crystallized from methanol, m.p. 232° dec, was identified with *isoretamine ethyl ether* (IIe) *diperchlorate* by its mixed m.p. and R_f number (NaOAc paper. Ba2. R_f = 0·88–KCl paper. Bc10. R_f = 0·64–Monopotassium phosphate paper. n-Butanol/water. R_f = 0·60).

4. *Chlororetamine nucleophilic substitutions and chloroisoretamine eliminations*

The same nucleophilic reagents, causing substitutions in chlororetamine, bring about eliminations with chloroisoretamine. Chlororetamine always yields isoretamine when treated with nucleophilic reagents containing the $H\bar{O}$ ion, whereas chloroisoretamine always affords Δ^{11}-dehydrosparteine with the same reagents.

Table 3 gives comparative experiments:

Chlororetamine reaction with sodium alcoholate. Chlororetamine monoperchlorate (0·5 g) was added to a solution of sodium (2 g) in anhydrous ethanol (30 ml). The solution was heated for 2½ hr and steam distilled. To the distillate (750 ml), perchloric acid was added (blue colour with Congo red) and the *isoretamine ethyl ether* (IIe) *diperchlorate* (0·48 g), crystallized from methanol, had m.p. 233–234° dec (Found: C, 42·8; H, 6·8; N, 5·6. $C_{15}H_{23}N_2OC_2H_5 \cdot 2ClO_4H$ requires: C, 42·6; H, 6·7; N, 5·8%).

The free base, an oil b.p. 125–127°/0·1 mm, was converted into *isoretamine ethyl ether monoperchlorate*, m.p. 155–156° (Found: C, 54·5; H, 7·4; N, 7·2. $C_{15}H_{23}N_2OC_2H_5 \cdot ClO_4H$ requires: C, 53·9; H, 8·2; N, 7·4%).

Cleavage of isoretamine ethyl ether diperchlorate (0·20 g) with boiling hydriodic acid (4 ml; sp. gr. 1·7) gave isoretamine (0·03 g) m.p. 161°.

Acknowledgements—We thank Professor Nelson J. Leonard (Urbana. Illinois, U.S.A.) for specimens of $\Delta^{11(15)}$-dehydrosparteinium diperchlorate and α-isosparteine, kindly sent to us, Dr. Guillermo García-Muñoz for his magnificent help in carrying out some reductions in sealed tube, Dr. J. Calderón, of Instituto "Alonso Barba" (Madrid), for many microanalysis, and Dr. J. Morcillo, of Instituto "A. G. de Rocasalano" (Madrid), for the infra-red spectra.

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STEREOCHEMICAL RELATIONS BETWEEN LYCORINE, CARANINE, PLUVIINE, AND LYCORENINE

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Abstract—Treatment of α-dihydrocaranine (VI) with ethanolic potassium hydroxide followed by hydrolysis of the resulting ethoxymethylether (VIII) and methylation with diazomethane afforded α-dihydropluviine (XII). The product, XVIII, obtained by the von Braun reaction of α-dihydrocaranine, was converted into α-deoxydihydrolycorenine (XXIII) without affecting asymmetric centres of the respective compounds. Thus the configurational relationship between lycorine, caranine, pluviine, and lycorenine have been clarified.

PLUVIINE[1] and lycorenine[2,3] are both alkaloids isolated from the bulbs of *Lycoris radiata* and other plants of Amaryllidaceae. Although the structures of these alkaloids have been established, very little was known of the stereochemistry until Uyeo *et al.*[4] recently assigned to them the configurations I and II respectively. The present author has worked independently on the stereochemistry of the alkaloids and this paper provides further evidence supporting these configurations.

In previous papers,[5,6] the configuration of dihydrolycorine was discussed and its absolute configuration (III) was recently established by Nakagawa and Uyeo[7]. Since caranine,[8–12] an alkaloid from Amaryllidaceae, was obtained by elimination of the hydroxyl group attached to carbon 2 of lycorine without any configurational change and likewise α-dihydrocaranine,[5,6] a hydrogenation product of caranine, was derived from dihydrolycorine, caranine and α-dihydrocaranine are structurally related to lycorine (IV) and dihydrolycorine, and configurations V and VI may be assigned to them respectively.

It has been established that the structure of pluviine differs from that of caranine by two methoxyl groups and a methylenedioxy group. Similarity of the behaviour of the two alkaloids toward a variety of reagents and biogenesis of this group of the alkaloids, indicates that pluviine and caranine, and α-dihydropluviine and α-dihydrocaranine, have similar configurations.

As proof, the conversion of the methylenedioxy group in α-dihydrocaranine into methoxyl groups under conditions which would not affect configurations of functional groups and the skeleton of the base was undertaken.

[1] H. G. Boit, S. Uyeo and H. Yajima, *Chem. Ber.* **90**, 363 (1957).
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[9] H. M. Fales, E. W. Warnhoff and W. C. Wildman, *J. Amer. Chem. Soc.* **77**, 5885 (1955).
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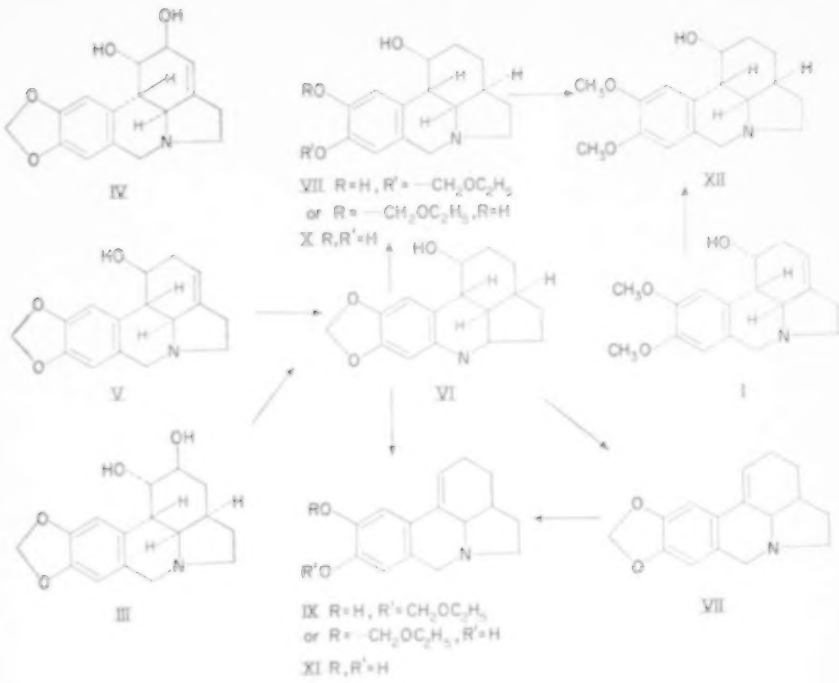


Attempts to cleave the methylenedioxy group in α-dihydrocaranine with aluminium chloride or bromide were not successful, but treatment of the base with ethanolic potassium hydroxide under nitrogen in a sealed tube gave a satisfactory result. The reaction mixture yields, along with α-anhydrodihydrocaranine (VII), two phenolic bases which were separated by chromatography and may be represented by the formulae VIII and IX, according to the result obtained by treatment of safrol[13–15] with the same reagents. It is highly improbable that any configurational changes take place during the reaction, since some starting material was recovered unchanged. Hydrolysis of the phenols VIII and IX, with hydrochloric acid afford demethylene-α-dihydrocaranine (X) and demethylene-α-anhydrodihydrocaranine (XI) respectively, characterized as hydrochlorides.

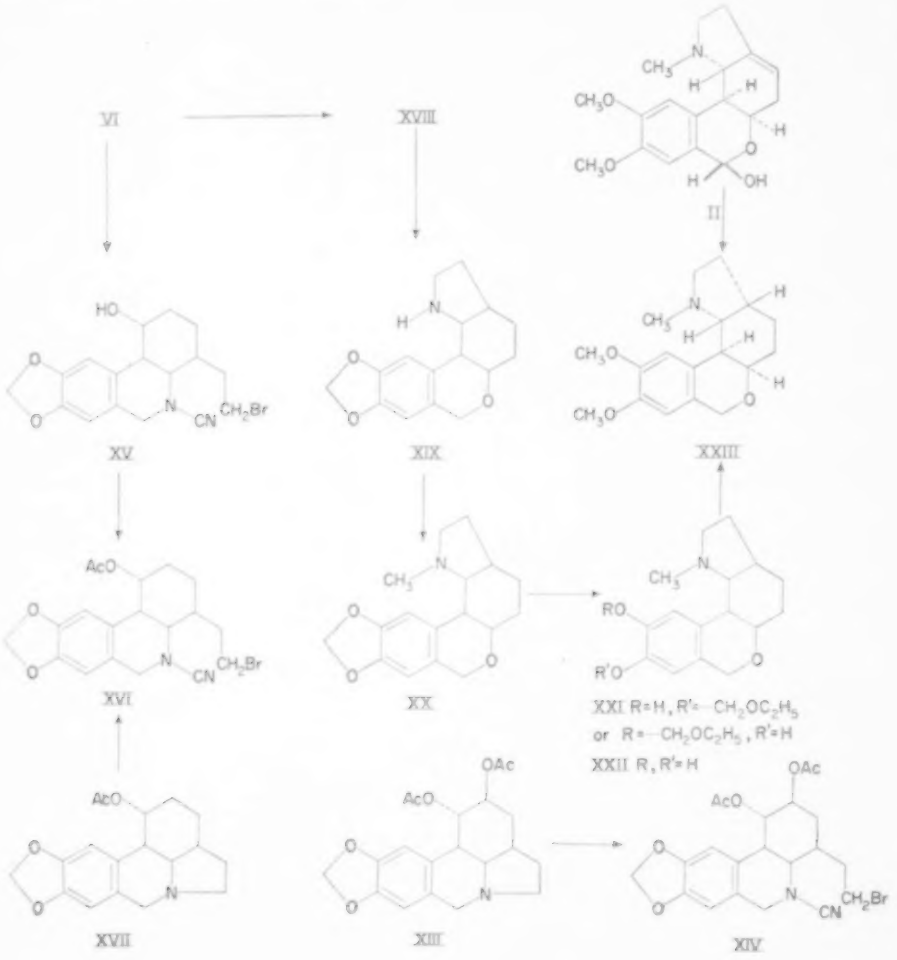
Both the phenols X and XI, give a green ferric chloride test and the analytical values, infra-red and ultra-violet spectra are in good agreement with the assigned structures. As expected, demethylene-α-anhydrodihydrocaranine (XI) is also obtained by treatment of α-anhydrodihydrocaranine (VII) with potassium hydroxide in ethanol in a sealed tube followed by hydrolysis with hydrochloric acid. Isolation of the free demethylene-α-dihydrocaranine from its hydrochloride failed, since the phenolic base is so soluble in water that it could not be extracted from its aqueous solution with organic solvents. Therefore, methylation of the free hydroxyl groups in demethylene-α-dihydrocaranine (X) was carried out with diazomethane using its hydrochloride in methanol. The resulting non-phenolic base is identical with α-dihydropluviine

[13] Hirao, *Nippon Kagaku Zasshi* **54**, 194 (1933).
[14] Hiraizumi, *Nippon Kagaku Zasshi* **55**, 605 (1934).
[15] Ono and Imoto, *Nippon Kagaku Zasshi* **59**, 364 (1933).

(XII). Thus the structural and configurational relationship between α-dihydropluviine (XII) and α-dihydrocaranine (VI) and between pluviine (I) and caranine (V) are verified.

An investigation was undertaken to cleave the pyrrolidine ring of α-dihydrocaranine (VI) by the von Braun reaction, analogous to that employed by Kondo and Katsura[16] for the fission of the pyrrolidine moiety of diacetyldihydrolycorine (XIII) to give diacetyl-ω-bromo-N-cyanodihydrosecolycorine (XIV) as the sole product.

Treatment of α-dihydrocaranine (VI) with cyanogen bromide in boiling benzene afforded, in contrast to the previous case, two products, $C_{17}H_{19}O_3N_2Br$ and $C_{17}H_{18}O_3N_2$ in a ratio of two to one.

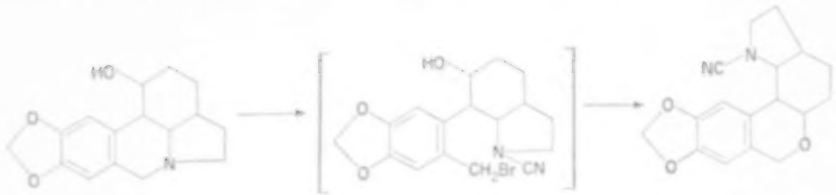


Compound XV contains bromine and exhibits infra-red absorptions at 4·48 and 2·90 μ characteristic of a CN and an OH group, respectively. The acetate (XVI) is

[16] H. Kondo and H. Katsura, *Yakugaku Zasshi* **59**, 733 (1939).

identical with the product obtained by the von Braun reaction of α-acetyldihydrocaranine (XVII).[11] Considering the similarity with diacetyl-ω-bromo-N-cyanodihydrosecolycorine (XIV) and the ease with which pyrrolidine rings can be cleaved with cyanogen bromide, structure XV is assigned to the compound, $C_{17}H_{19}O_3N_2Br$.

On the other hand, $C_{17}H_{18}O_3N_2$ isolated from the mother liquors of XV shows a CN band in the infra-red spectrum at 4·54 μ but neither a hydroxyl nor a carbonyl band could be detected. Since two oxygen atoms in the molecule belong to a methylenedioxy group, the remaining third oxygen is considered present as an ether group. In view of this, it seemed plausible that the compound XVIII results from cleavage of the piperideine instead of the pyrrolidine ring in α-dihydrocaranine (VI) followed by elimination of hydrogen bromide to give an oxygen bridge as follows:



VI XVIII

Unequivocal evidence for this structure is given by the following reactions: Treatment of $C_{17}H_{18}O_3N_2$ with lithium aluminium hydride in ether gives in good yield a basic product (XIX), $C_{16}H_{19}O_3N$, which exhibits a NH band in the infra-red spectrum at 3·00 μ but no CN absorption.

Methylation of the secondary amine XIX with formaldehyde and formic acid affords the N-methyl derivative XX, $C_{17}H_{21}O_3N$, which was treated in a sealed tube with ethanolic potassium hydroxide at 180–190° as mentioned for the cleavage of the methylenedioxy group in α-dihydrocaranine. The resulting XXI exhibits no infra-red absorptions typical of a methylenedioxy group at about 9·6 and 10·7 μ but a hydroxyl band at 2·78 μ. Hydrolysis with dilute hydrochloric acid of XXII gives a dihydroxy derivative characterized as the hydrochloride and giving a green ferric chloride test. Methylation of the phenolic hydroxyl groups was accomplished by treatment of the base with excess ethereal diazomethane, giving a non-phenolic base, $C_{18}H_{25}O_3N$, m.p. 123–124°, $[\alpha]_D$ −18·7°, which is identical with α-deoxydihydrolycorenine (XXIII) in m.p., mixed m.p., optical rotation and infra-red spectrum.

Since in the conversion of α-dihydrocaranine (VI) into α-deoxydihydrolycorenine (XXIII) no asymmetric centre was affected, the stereochemical relationship between these two bases is established and the configurations of α-deoxydihydrolycorenine and lycorenine can be deduced from that of α-dihydrocaranine (VI) and represented by formulae XXIII and II. The experimental evidence establishes that the asymmetric carbons in caranine (V), pluviine (I), and lycorenine (II) have the same configuration as those in lycorine (IV), which is in accordance with the accepted biogenesis of these alkaloids.

EXPERIMENTAL

Melting points are not corrected.

Methylenedioxy ring-opening of α-dihydrocaranine (VI) *with ethanolic potassium hydroxide.*

KOH (750 mg) was added to a solution of α-dihydrocaranine (VI, 600 mg) in 95% ethanol (25 ml). The reaction mixture was heated under nitrogen in a sealed tube at 180–190° for 1·5 hr. The solvent was removed under reduced pressure and the residue divided into benzene- and water-soluble fractions. Evaporation of the dried benzene left a colourless oil (210 mg) which gave on crystallization from ethanol, unchanged α-dihydrocaranine (100 mg) m.p. 165–168°, undepressed on admixture with the starting material. The mother liquor was chromatographed in benzene over alumina. The benzene eluate yielded α-anhydrodihydrocaranine (VII, 60 mg) as needles, m.p. 83–84°, identical in m.p. and infra-red spectrum with the authentic sample obtained by Takeda and Kotera. On further elution with chloroform, additional unchanged α-dihydrocaranine (20 mg) was recovered. The water-soluble fraction was filtered, saturated with ammonium chloride, and extracted with chloroform. Concentration of the dried extract gave a brown oil (425 mg) which was dissolved in chloroform–benzene (6:1) and chromatographed on alumina (20 g). Elution with chloroform–benzene (6:1) gave a colourless oil which could not be crystallized. Treatment with 5% HCl gave after crystallization from water, 40 mg of the hydrochloride of XI as needles, m.p. 260° (decomp); $[\alpha]_D^{27}$ −34° (*c*, 0·42 in 70% ethanol); λ_{max} 263, 306 mμ; log ε, 4·06, 3·66; λ_{max} 2·95, 2·97 (OH), 6·20 μ. This gave a green ferric chloride test. (Found: C, 62·62; H, 6·64; N, 5·10. $C_{18}H_{17}O_3N{\cdot}HCl{\cdot}1/2H_2O$ requires: C, 62·39; H, 6·63; N, 4·85%).

Further elution with chloroform–methanol (50:1 and 30:1) gave colourless oil (300 mg) which could not be crystallized. Treatment with 5% HCl gave the hydrochloride of X, (287 mg) m.p. 250–255° (decomp). The analytical sample was obtained by recrystallization from water, m.p. 267–270° (decomp); $[\alpha]_D^{27}$ −56° (*c*, 0·26 in 70% ethanol); λ_{max} 285 mμ; log ε, 3·78; λ_{max} 2·93 (OH), 6·21 μ. (Found: C, 58·72; H, 7·00; N, 4·72. $C_{19}H_{21}O_3N{\cdot}HCl{\cdot}1/2H_2O$ requires: C, 58·72; H, 6·89; N, 4·57%).

Attempts to isolate the free phenolic base from the hydrochloride of X failed, since it could not be extracted from its aqueous solution by a variety of solvents. The picrate was prepared in dilute ethanolic solution and crystallized from ethanol as yellow plates, m.p. 201–202°. (Found: C, 49·95; H, 4·79; N, 11·00. $C_{19}H_{21}O_3N{\cdot}C_6H_3O_7N_3{\cdot}H_2O$ requires: C, 49·61; H, 4·76; N, 11·02%).

Methylenedioxy ring-opening of α-anhydrodihydrocaranine with ethanolic potassium hydroxide. α-Anhydrodihydrocaranine (VII; 300 mg) was treated with KOH (375 mg) in 95% ethanol (12 ml) as for α-dihydrocaranine. α-Anhydrodihydrocaranine (136 mg), m.p. and mixed m.p. 83–85°, was recovered unchanged. The phenolic fraction was chromatographed on alumina (5 g). Elution with chloroform–benzene (1:1, 2:1, 3:1, 4:1, 5:1 and 6:1) gave a colourless oil (110 mg) which was hydrolysed with HCl to give after concentration the hydrochloride of XI (80 mg) as needles, m.p. 257–261° (decomp), identical with the phenolic by-product obtained by treatment of α-dihydrocaranine with potassium hydroxide as described above.

Methylation of demethylene-α-dihydrocaranine (X) *with diazomethane.* To a solution of the hydrochloride of X (200 mg) in methanol (25 ml) was added ethereal diazomethane (150 ml) prepared from nitrosomethylurea (10 g). The mixture was kept at room temp for 4 days. Excess of the diazomethane was decomposed with dil HCl, the mixture concentrated and the resulting oil dissolved in dil HCl, filtered and basified with 10% NaOH. Extraction with benzene and evaporation after washing with 10% NaOH and drying gave a brown oil (70 mg), which was chromatographed in benzene on alumina (5 g). Elution with benzene–ethyl acetate (5:1 and 4:1) gave α-dihydropluviine (XII, 20 mg). The analytical sample, m.p. 135–137°, recrystallized from acetone, $[\alpha]_D^{21}$ −83·4° (*c*, 0·31 in ethanol); λ_{max} 232, 282 mμ; log ε; 3·79, 3·62, was identical by mixed m.p. and infra-red spectrum with an authentic specimen. (Found: C, 70·30; H, 8·12; N, 4·58. Calc. for $C_{17}H_{23}O_3N$: C, 70·56; H, 8·01; N, 4·84%).

Reaction of α-dihydrocaranine (VI) *with cyanogen bromide.* A solution of cyanogen bromide (250 mg) in dry benzene (8 ml) was added dropwise to a solution of α-dihydrocaranine (VI, 500 mg) in dry benzene (42 ml) and the mixture refluxed for 3 hr. The reaction mixture was washed with water, 5% HCl and again with water, and concentrated to 1/3 of its volume with separation of XV as needles (138 mg). The analytical sample m.p. 183–185° recrystallized from ethanol, $[\alpha]_D^{25}$ −173·4° (*c*, 0·51 in chloroform); λ_{max} 237, 291 mμ; log ε, 3·68, 3·70; λ_{max} 2·91 (OH), 4·49 μ (N–CN). (Found: C, 54·05; H, 5·07; N, 7·22; Br, 20·86. $C_{17}H_{19}O_3N_2Br$ requires: C, 53·83; H, 5·05; N, 7·39; Br, 21·08%).

The mother liquors from the above crystals were evaporated and the resulting brown oil dissolved in benzene and chromatographed on alumina (15 g). Elution with benzene afforded XVIII (125 mg)

which recrystallized from ethanol as colourless prisms, m.p. 187–188°; $[\alpha]_D^{16}$ −135·9° (*c*, 0·38 in chloroform); λ_{max} 236, 290 mμ; log ε, 3·64, 3·65; λ_{max} 4·54 μ (N–CN). (Found: C, 68·30; H, 6·30; N, 9·05. $C_{17}H_{14}O_3N_2$ requires: C, 68·44; H, 6·08; N, 9·39%). Further elution with benzene–ethyl acetate (3:1) gave additional XV (73 mg) as colourless needles, m.p. 183–185°.

Reaction of α*-acetyldihydrocaranine* (XVII) *with cyanogen bromide.* A solution of cyanogen bromide (250 mg) in dry benzene (4 ml) was added dropwise to a solution of α-dihydroacetylcaranine (XVII, 250 mg) in dry benzene (6 ml) and refluxed for 1 hr. The product (XVI, 230 mg) recrystallized from ethanol as colurless needles, m.p. 158°; $[\alpha]_D^{21}$ −127·4° (*c*, 0·58 in chloroform); λ_{max} 237, 291 mμ; log ε, 3·68, 3·71; λ_{max} 4·53 (N–CN), 5·79 μ (−$OCOCH_3$). (Found: C, 53·72; H, 5·22; N, 6·56; Br, 18·75. $C_{15}H_{15}O_4N_2Br$ requires: C, 54·15; H, 5·02; N, 6·65; Br, 18·98%).

Acetylation of XV. A solution of XV (150 mg) in dry pyridine (0·5 ml) and acetic anhydride (1 ml) was allowed to stand at room temp for 24 hr. The reaction mixture was poured into ice-cold water, basified with 10% aqueous sodium carbonate and extracted with benzene. Concentration of the dried extract gave the acetate (XVI, 100 mg) which after crystallization from ethanol, gave colourless needles, m.p. and mixed m.p. 158°. The infra-red spectrum in Nujol was also identical with that of XVI.

Reduction of XVIII *with lithium aluminium hydride.* A solution of XVIII (97 mg) in dry ether (70 ml) was refluxed with lithium aluminium hydride (200 mg) for 3 hr. After addition of water, the precipitate was filtered off and the filtrate and washings combined, dried and evaporated to give colourless needles (86 mg). Recrystallization from ethanol gave XIX (76 mg), m.p. 139–140°; $[\alpha]_D^{19}$ −6·5° (*c*, 0·42 in ethanol); λ_{max} 292 mμ; log ε, 3·66; λ_{max} 3·00 μ (N–H). (Found: C, 70·02; H, 7·11; N, 4·97. $C_{16}H_{13}O_3N$ requires: C, 70·31; H, 7·01; N, 5·13%).

The Eschweiler–Clarke reaction of XIX. A mixture of XIX (95 mg), 85% formic acid (0·2 ml) and 37% formalin (0·05 ml) was refluxed for 6 hr. The mixture was then evaporated to dryness under reduced pressure, taken up in 5% HCl, filtered, basified with 10% aqueous sodium carbonate and extracted with benzene. Concentration of the dried extracts gave an oil (99 mg), which was taken up in light petroleum and chromatographed on alumina (5 g). Elution with light petroleum gave a crystalline product, which on recrystallization from light petroleum gave colourless prisms (XX, 79 mg) m.p. 82–84°; $[\alpha]_D^{19}$ +2° (*c*, 1·01 in ethanol); λ_{max} 292 mμ; log ε, 3·67. (Found: C, 71·08; H, 7·08; N, 4·80. $C_{17}H_{21}O_3N$ requires: C, 71·05; H, 7·37; N, 4·87%).

Methylenedioxy ring-opening of XX *with ethanolic potassium hydroxide.* A solution of XX (154 mg) and KOH (187 mg) in 95% ethanol (4 ml) was heated under nitrogen in a sealed tube at 180–190° for 1·5 hr. The mixture was concentrated to dryness under reduced pressure and the residue in water extracted with light petroleum. Concentration of the dried extract recovered unchanged starting material (30 mg). The aqueous layer was saturated with ammonium chloride and extracted with chloroform and dried. The residue was chromatographed in benzene on alumina (10 g). Elution with benzene afforded a crystalline product (120 mg) which was recrystallized from ether as colourless needles (XXI, 90 mg) m.p. 96–98°; $[\alpha]_D^{20}$ +30·7° (*c*, 0·55 in ethanol); λ_{max} 285 mμ; log ε, 3·40; λ_{max} 2·78 μ (OH), 6·25 μ. (Found: C, 68·64; H, 8·36; N, 3·96. $C_{18}H_{27}O_4N$ requires: C, 68·44; H, 8·16; N, 4·20%).

Action of hydrochloric acid on XXI. A solution of XXI (50 mg) in dil HCl was heated at 100° for a few min. The mixture was filtered, evaporated to dryness, and the residue crystallized from water to give the hydrochloride of XXII as colourless scales, m.p. 235–240° (decomp); $[\alpha]_D^{21}$ −37° (*c*, 0·81 in 70% ethanol); λ_{max} 288 mμ; log ε, 3·57. (Found: C, 61·42; H, 7·20; N, 4·41. $C_{16}H_{21}O_3N{\cdot}HCl$ requires: C, 61·60; H, 7·11; N, 4·49%).

Methylation of XXII *with diazomethane.* After refluxing XXI (140 mg) in 5% HCl (3 ml) for a few min, the mixture was basified with aqueous ammonia and extracted with ether. Concentration of the dried extract gave an oil (XXII, 100 mg) which in ether (10 ml) was treated with ethereal diazomethane (80 ml) prepared from nitrosomethylurea (5 g). After being kept at room temp for 4 days, the mixture was concentrated to dryness, the residue in ether, filtered and treated again with excess diazomethane for further 4 days. The excess diazomethane was destroyed by dropwise addition of 5% HCl, the ether evaporated, and the residue in dil HCl, filtered and basified with 10% aqueous sodium carbonate. Extraction with benzene and removal of the solvent afforded a residue (98 mg) which was chromatographed in benzene–light petroleum (1:1) on alumina (5 g). The benzene–light petroleum (1:1) eluate gave a crystalline product (XXIII, 30 mg) m.p. 118–120°. Three recrystallizations from methanol gave colourless needles, m.p. 123–124°; $[\alpha]_D^{16}$ −18·7° (*c*, 0·39 in ethanol); λ_{max}

285 mμ; log ε, 3·70. (Found: C, 71·05; H, 8·09; N, 4·64. Calc. for $C_{15}H_{25}O_3N$: C, 71·25; H, 8·31; N, 4·62%).

This was identical in m.p., mixed m.p., optical rotation and infra-red spectrum with authentic α-deoxydihydrolycorenine furnished by Prof. Uyeo. Further elution with chloroform and chloroform–methanol (10:1) gave a phenolic oil (40 mg) which was further methylated with diazomethane to α-deoxydihydrolycorenine (14 mg).

Acknowledgements—The author wishes to express his deep appreciation to Dr. K. Takeda, Director of this Laboratory, and to Prof. S. Uyeo of the University of Osaka for their valuable discussions.

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RESONANCE AND CONJUGATION—II[1]

FACTORS DETERMINING BOND LENGTHS AND HEATS OF FORMATION

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(*Received* 23 *February* 1960; *in revised form* 16 *May* 1960)

Abstract—Two previous papers[1,3] presented interim reports of an investigation into the importance of resonance in conjugated systems. Further work has confirmed our earlier conclusions that resonance effects are unimportant in classical molecules, the bond lengths in them being determined by the state of hybridization of carbon; that the observed stabilization of such molecules is due to changes in bond energy with hybridization rather than to resonance; and that resonance stabilization plays a surprisingly small role even in benzene. A calculation is described which, starting from very limited experimental data, provides values for several CC bond lengths (ethylene, benzene, graphite) which agree excellently with experiment, a value for the sp^2–sp^3 C—C bond length which agrees well with the value found in butadiene, diphenyl, etc., and a set of bond energies for CC and CH bonds of various types. Heats of formation for a number of hydrocarbons are calculated from these bond energies and compared with experiment. Agreement is excellent for paraffins, olefines, and acetylenes, confirming the lack of hyperconjugative stabilization in the latter. Deviations in cycloparaffins are ascribed to conformational effects (CH—CH dipole repulsions). Butadiene shows an apparent resonance energy of 2 kcal/mole, less than a quarter of the stabilization energy; reasons are given for believing even this value to be much too large. The lack of resonance in butadiene is confirmed by a MO calculation of its effect on the bond lengths. When allowance is made for the effect of σ-bond compression, the resonance energy of benzene is found to be only about 10 kcal/mole, less than a quarter of the stabilization energy. Previous ideas [1,3] concerning the importance of electron correlation in conjugated systems are clarified: it is shown that the neglect of such correlation invalidates existing methods of calculation, particularly in the case of classical molecules, and a method is suggested whereby such correlation effects might be taken into account. The significance of resonance theory is discussed. Various criticisms made by Mulliken in a recent paper[4] are shown to be unjustified.

THIS paper describes a general investigation into the factors determining bond lengths and heats of formation in conjugated systems. Preliminary accounts[1,3] were given in Paris in September, 1957, at the C.N.R.S. Colloquium on the calculation of molecular wave functions, and at Bloomington in June, 1958, at the Conference on Hyperconjugation. These earlier studies led to the conclusion that, in contrast to most current opinion, resonance effects are relatively unimportant in classical* molecules and that the arguments commonly cited as evidence for resonance in such molecules are vitiated by their neglect of changes in the properties of carbon bonds with hybridization. Here we present the results of our completed investigation. This has not only confirmed our earlier conclusions but it has also provided further cogent

* A classical molecule is defined as one for which only a single classical (unexcited) resonance structure can be written; e.g. CH_2=CH—CH=CH_2, CH_3—C≡CH.

[1] Part I: M. J. S. Dewar and H. N. Schmeising, *Tetrahedron* **5**, 166 (1959).
[2] Department of Chemistry, Illinois Institute of Technology, Chicago 16, Illinois.
[3] M. J. S. Dewar and H. N. Schmeising, *Collogues Internationaux du Centre National de la Recherche Scientifique* **82**, 51 (1958).

evidence that resonance effects are very generally of less importance than has commonly been supposed.

1. *Lengths of carbon bonds*

We argued in Part I[1] that the available data on carbon bond lengths could be explained in terms of changes in effective covalent radius of carbon with its state of hybridization. The idea that bond lengths should vary with hybridization was put forward some years ago by Walsh[4] and by Coulson[5]; but subsequent authors have agreed with Coulson's[5] conclusion that the changes in covalent radius are not sufficient to account for the observed changes in bond length, and that resonance effects must also be important.

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If the lengths of single bonds C—X between carbon and some other atom X are determined only by the state of hybridization of carbon, one might expect the length to vary more or less linearly with the percentage *s*-character of carbon,* the length of a given type of bond being always the same. By an obvious extension, one would expect the lengths of carbon–carbon bonds to be a linear function of the mean percentage *s*-character of the two carbon atoms, the length of a given type of bond always being the same. These relations would not be expected to hold if resonance effects were important; for the resonance interactions would involve bonds adjacent to the bond in question. One would not expect the resonance interaction between the CH and CC bonds in $C:H_3—C:CH$ to be the same as that between CCl and C:N bonds in $CCl_3—C:N$, and so one would not expect the C—C single bonds to have the same length if resonance were important.

Herzberg and Stoicheff[7] pointed out some years ago that the data then available suggested that the lengths of C—C single bonds in acetylenes depend only on the state (saturated or acetylenic) of the terminal carbon atoms. Table 1 lists all the accurate data now available for C—C single bonds of various types. All the values were derived from spectroscopic measurements except those for the sp^2–sp^2 bonds; these were measured by Bastiansen *et al.* using refined electron diffraction techniques. Note that the lengths of the sp^3–sp and sp–sp bonds are remarkably constant, confirming the earlier work.[7] These values should be accurate to a few thousandths of an angstrom. The rather scanty data for sp–sp^2 and sp^2–sp^2 bonds are subject to larger errors.

The mean lengths for the bonds of various types (last column of Table 1) are plotted against percentage *s*-character of carbon in Fig. 1. The value assumed for the sp^2–sp^3 bond (1·544 Å) is that observed in diamond; that for the sp^2–sp^3 bond (1·515 Å) is the mean of fourteen recent[8] X-ray determinations. All six points are seen to lie close to a straight line.

The data listed in Table 1 and Fig. 1 strongly suggest that the lengths of C—C single bonds in classical molecules, even in conjugated molecules such as diacetylene

* This argument has been misquoted by Professor R. S. Mulliken in a recent criticism[6] of our work. The shortening in passing from sp^3 carbon (25% *s*) to sp^2 carbon (33–1/3% *s*) should not be the same as that in passing from sp^2 to *sp* carbon (50% *s*); the second contraction should be—and is—about double the first.

[4] A. D. Walsh, *Trans. Faraday Soc.* **43**, 60 (1957).
[5] C. A. Coulson, *Victor Henri Memorial Volume* p. 15. Desoer, Liège (1948); cf. *J. Phys. Chem.* **56**, 311 (1952).
[6] R. S. Mulliken, *Tetrahedron* **6**, 68 (1959).
[7] L. F. Herzberg and B. P. Stoicheff, *Nature, Lond.* **175**, 79 (1955).
[8] L. E. Sutton, *Tables of Interatomic Distances*. Special Publication No. 11 of The Chemical Society, London (1958).

TABLE 1. LENGTHS OF C—C SINGLE BONDS IN CLASSICAL MOLECULES

Compound	Type of bond	Length (Å)	Mean length (Å) of bonds of given type
CH_3—C≡CH	sp–sp^3	1·459[a]	
CH_3—C≡CCl	sp–sp^3	1·458[b]	
CF_3—C≡CH	sp–sp^3	1·464[b]	
$ClCH_2$—C≡CH	sp–sp^3	1·458[c]	
CF_3—C≡C—CH_3	sp–sp_3	1·455[d]	
CH_3—C≡N	sp–sp^3	1·458[a]	
CF_3—C≡N	sp–sp^3	1·464[b]	
CCl_3—C≡N	sp–sp^3	1·460[e]	
CH_3—C≡C—C≡N	sp–sp^3	1·458	1·459
	sp–sp	1·379[b]	
HC≡C—C≡CH	sp–sp	1·379[b]	
HC≡C—C≡N	sp–sp	1·378[a]	
N≡C—C≡N	sp–sp	1·380[b]	1·379
CH_2=CH—C≡CH	sp–sp^2	1·446[f]	
CH_2=CH—C≡N	sp–sp^2	1·426[f]	
O=CH—C≡CH	sp–sp^2	1·445[g]	1·439
CH_2=CH—CH=CH_2	sp^2–sp^2	1·483[h]	
diphenyl	sp^2–sp^2	1·492[i]	
4:4'-dipyridyl	sp^2–sp^2	1·470[i]	1·482

[a] C. C. Costain, *J. Chem. Phys.* **29,** 864 (1958).
[b] L. E. Sutton, *Tables of Interatomic Distances.* Special Publication No. 11 of The Chemical Society, London (1958).
[c] E. Hirota, T. Oka and Y. Morino, *J. Chem. Phys.* **29,** 444 (1958).
[d] B. Bak, D. Christiansen, L. Hausen-Nygaard and E. Tannenbaum, *J. Chem. Phys.* **26,** 134 (1957).
[e] J. B. Baker, D. R. Jenkins, C. W. Kenney and T. M. Sugden, *Trans. Faraday Soc.* **53,** 1397 (1957).
[f] C. C. Costain and B. P. Stoicheff, *J. Chem. Phys.* **30,** 777 (1959).
[g] C. C. Costain and J. R. Morton, *J. Chem. Phys.* **31,** 389 (1959).
[h] A. Almenningen, O. Bastiansen and M. Traetteberg, *Acta Chem. Scand.* **12,** 1221 (1958).
[i] (values for the central bond) A. Almenningen and O. Bastiansen, *Kgl. Norske Videnskab. Selskabs. Skrifter* No. 4, 1 (1958).

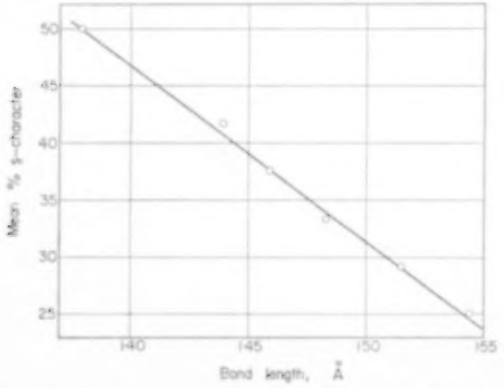

FIG. 1. Plot of bond lengths vs. mean percentage s-character of carbon for C—C single bonds.

or butadiene, depend only on the state of hybridization of carbon and are little affected by resonance.*

* The multiple bonds also show no variation in length greater than the limits of experimental error; this, however, is less significant since it is well known that current theory predicts much smaller increases in length of multiple bonds in resonating systems than decreases in the lengths of single bonds; cf. H. C. Longuet-Higgins and F. H. Burkitt, *Trans. Faraday Soc.* **48,** 1077 (1952).

It is a pity that so few accurate determinations are available for the lengths of other bonds. Some recent values for CH, CCl, CBr, and Cl bonds are listed in Table 2 and plotted against percentage *s*-character of carbon in Fig. 2. In each case the points for sp^3, sp^2, and *sp* carbon lie accurately on a straight line.

TABLE 2. LENGTHS OF CH, CCl, CBr, AND Cl BONDS OF VARIOUS TYPES

Hybridization of carbon	H	Length of C—X bond (Å): X =		
		Cl	Br	I
sp^3	1·102[a]	1·781[d]	1·939[d]	2·139[d]
sp^2	1·086[b]	1·736[e]	1·891[e]	2·092[e]
sp	1·057[c]	1·637[c]	1·739[a]	1·991[e]

[a] bond lengths in C_2H_6, CH_2:CHCl, CH_2:CHBr, CH_2:CHI, MeC ⋮ CBr, MeC ⋮ Cl; L. E. Sutton, *Tables of Interatomic Distances*. Special Publication No. 11 of The Chemical Society, London (1958).
[b] bond length in C_2H_4; see ref.[15–17]
[c] bond length in C_2H_2; J. H. Callomon and B. P. Stoicheff, *Canad. J. Phys.* **35**, 373 (1957).
[d] bond lengths in CH_3Cl, CH_3Br, CH_3I; C. C. Costain, *J. Chem. Phys.* **29**, 864 (1958).
[e] bond length in MeCC ⋮ Cl; C. C. Costain, *J. Chem. Phys.* **23**, 2037 (1955).

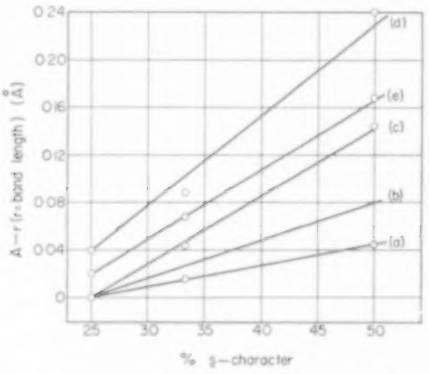

FIG. 2. Plot of bond length vs. percentage *s*-character of carbon for C—X bonds:
(a) X = H, A = 1·102; (b) X = C, A = 1·540; (c) X = Cl, A = 1·781;
(d) X = Br, A = 1·979; (e) X = I, A = 2·159.

These results suggest that the lengths of CH, CCl, CBr, and Cl bonds are also determined by the state of hybridization of carbon rather than by resonance; this agrees with the conclusion reached from measurements of nuclear quadrupole coupling constants[9] that the C—Cl bond in vinyl chloride has little double bond character (ca. 5%).

As we pointed out in Part I,[1] this argument seems open to criticism in that one would expect the lines in Fig. 2 to be parallel if the rule of additivity of covalent radii held. Mulliken has stressed this point in his criticism[6] of our work. However the rule of additivity of covalent radii has no good theoretical basis and numerous experimental exceptions to it are known—as we pointed out in Part I.[1] The following argument shows that one would not expect it to hold except as a rough first approximation, and that the results indicated in Fig. 2 are consistent with the idea that the

[9] J. H. Goldstein, *J. Chem. Phys.* **24**, 106 (1956).

bond lengths plotted there are determined almost entirely by changes in hybridization of carbon.

Accepting the criterion of maximum overlap,[10] we would expect the variation in length of carbon bonds with hybridization to reflect changes in size and shape of the carbon hybrid AO. If the atom X forming a bond C—X is much smaller than carbon, overlap will be best if the AO of X is centred at the point of maximum density of the carbon AO. If on the other hand X is much larger than carbon, overlap will be best when the centre of gravity of the carbon AO is centred at the point of maximum density of the AO of X. Therefore in the first case the change in bond length with hybridization of carbon should parallel changes in the distance from the carbon nucleus to the *point of maximum orbital density* in its AO, in the second case it should parallel changes in the distance from the carbon nucleus to the *centre of gravity* of its AO. There is no reason why these two distances should change in the same way with hybridization.

Note that the plots in Fig. 2 for bonds to Cl, Br, and I all atoms which are much larger than carbon, are approximately parallel; this would be expected from the argument given above. It is not surprising to find a different result for CH bonds, H being much smaller than carbon; and it is satisfactory to find that the slope for the intermediate case of carbon–carbon bonds (X = C) is intermediate between the extremes when X is much smaller, or much larger, than carbon.

This argument shows that the rule of additivity of covalent radii should not be expected to hold accurately and that attempts to explain away small deviations from it are misguided. It is perhaps unfortunate that so much confidence has been placed on a rule based on inaccurate data and lacking any valid theoretical justification.

It should be added that since publication of our previous papers[1,3] several other authors have come out in support of the idea that resonance effects are unimportant in classical molecules. Costain and Stoicheff[11] pointed out that the lengths of a C—C bond depends only on the number of atoms or groups attached to the carbon atoms forming the bond; this number is determined by the state of hybridization of the two carbon atoms. Brown[12] and Somayajulu[13] have concluded that the lengths of such bonds are determined by the hybridization of the carbon atoms and not by resonance. Bartell[14] suggests that the bond lengths are determined by Van der Waal's interactions between the adjacent groups; although this interesting idea seems to differ from that proposed here, Professor Bartell at any rate agrees with us in ascribing little importance to resonance. A detailed analysis of the relation between non-bonded interactions and hybridization would be of interest.

II. *The bond order–bond length relation*

We pointed out in our previous papers[1,3] that if the CC bond lengths in ethylene, benzene, and graphite are plotted against their π-bond orders (found using LCAO MO coefficients calculated with inclusion of overlap; cf. Appendix 3. Thus the π-bond order for ethylene is $(1 + S)^{-1}$), the three points lie approximately on a straight line which extrapolates to a value ca. 1·47 Å for zero π-bond order. Since that time the

[10] R. S. Mulliken, *J. Amer. Chem. Soc.* **72**, 4493 (1950).
[11] C. C. Costain and B. P. Stoicheff, *J. Chem. Phys.* **30**, 777 (1959).
[12] M. G. Brown, *Trans. Faraday Soc.* **55**, 694 (1959).
[13] G. R. Somayajulu, *J. Chem. Phys.* **31**, 919 (1959).
[14] L. S. Bartell, *J. Amer. Chem. Soc.* **81**, 3497 (1959).

length of the CC bond in ethylene has been redetermined and found to be nearly 0·02 Å less than the "old" value. With the new values 1·333,[15] 1·337,[16] or 1·339,[17] Å, the points for ethylene, benzene, and graphite become accurately collinear, extrapolating to a value (1·488 Å) which is within experimental error of the observed length (1·483 Å) of the central bond in butadiene (Fig. 3). This suggests that the length of a single bond between sp^2 carbon atoms is about 1·485 Å, and that the bond order–bond length plot is linear, the curvature in published plots being due to the neglect of changes in bond length with hybridization and the consequent assumption that the bond length for zero bond order is 1·54 Å. Brown[12] has independently reached the same conclusion.

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III. *Heats of formation and bond energies*

(a) *General considerations and terminology.* In Part I[1] we pointed out that if the lengths of carbon bonds vary with hybridization, so also must their bond energies; and that in this case current calculations of "resonance energies" would have no significance, since they neglect such changes in bond energy with hybridization. We also criticized the calculation of resonance energies by comparison of the heats of hydrogenation of conjugated compounds with those of partial reduction products (e.g. butadiene with 1-butene, benzene with cyclohexene). These "reference compounds" are themselves stabilized by a structural feature (presence of a saturated carbon next to a multiple bond) which is not present in the conjugated original. Whether or not this stabilization is a resonance effect ("hyperconjugation") is entirely irrelevant; the "resonance energies" calculated in this way are a meaningless conglomeration of two different effects, one of which does not appear in the parent conjugated system.

We suggested as a measure of the stabilization of an unsaturated molecule a comparison of its heat of formation with that of an equivalent number of simple molecules (e.g. ethylene, acetylene) where no resonance can occur. Following Mulliken we termed this purely empirical quantity the *stabilization energy* (*SE*). The chemical behaviour will be determined by the stabilization energy, rather than by the fictitious resonance energies estimated by current methods.

We showed that the stabilization energy of butadiene must contain a component δH due to changes in bond energy with hybridization, and given by

$$\delta H = (E' - E) - 2(\epsilon' - \epsilon) \qquad (1)$$

where E', E are respectively the bond energies of C—C bonds between sp^2 and sp^3 carbon atoms, and ϵ', ϵ are the corresponding CH bond energies. We showed that the whole of the observed stabilization energy of butadiene might be explained in this way,* resonance stabilization being negligible. The same is true for "hyperconjugated" molecules such as propene.

This implies that the chemically very significant stabilization in such molecules may not be due to resonance; in this case there is a real need for terms to describe

* We must draw attention to a further misquotation in Professor Mulliken's paper.[5] We did not postulate[1] that $\epsilon' = \epsilon$; we postulated only that $(E' - E) > 2(\epsilon' - \epsilon)$, on the grounds that if CC bonds vary in length more with hybridization than do CH bonds (cf. Fig. 2 in this paper) they should show correspondingly greater changes in bond energy with hybridization.

[15] L. S. Bartell and R. A. Bonham, *J. Chem. Phys.* **31**, 400 (1959).
[16] H. C. Allen and E. K. Plyler, *J. Amer. Chem. Soc.* **80**, 2673 (1958).
[17] J. M. Dowling and B. P. Stoicheff, quoted by Costain and Stoicheff[15].

the structural features leading to such stabilization without any reference to their cause. The term "conjugation" has always had a structural connotation in organic chemistry; here one need only abandon its improper identification with resonance. The term "hyperconjugation" has, however, always been used in the literature in its original sense, implying[18] a special type of resonance interaction. We wish to suggest the term *semiconjugation* to describe the corresponding structural feature. Thus conjugation implies the presence of a single C—C bond between unsaturated carbon atoms, semiconjugation the presence of a bond between a saturated and an unsaturated carbon atom.

The next problem is to determine how much, if any, of the stabilization energies of conjugated and semiconjugated molecules are to be ascribed to resonance. To do this one needs to know the various bond energies involved [cf. equation (1)].

We first tried to estimate bond energies directly, by equating the calculated and observed heats of formation of a number of hydrocarbons and solving the resulting set of equations for the bond energies. This attempt failed for technical reasons (see Appendix 1), an unfortunate circumstance, since if successful it would have provided directly an unambiguous set of bond energies.

We therefore adopted the expedient of assuming relations between bond energy and bond length for CC and CH bonds. Glockler[19] and Feilchenfeld[20] have proposed relations of this kind in which bond energy (E) is expressed as a power of, or power series in, r^{-1}, r being the bond length. Their work was, however, based on the "old" value (1·353 Å) for the length of the C:C bond in ethylene. When we tried to repeat their calculations using the newer values[15–17] of 1·333–1·339 Å we could not obtain satisfactory results.

If there is a relation between bond energy and bond length, it must be such that E is finite at $r = 0$ and vanishes as $r \to \infty$, and it must satisfy everywhere the conditions.

$$\frac{\partial E}{\partial r} < 0; \quad \frac{\partial^2 E}{\partial r^2} > 0; \quad E > 0 \quad (r > 0) \tag{2}$$

Glockler's function does not fulfil these conditions when the new value for the ethylene bond length is used; while Feilchenfeld's relation cannot be made to fit the data. Even a five-term polynomial in r^{-1} proved unsatisfactory.

The obvious solution was to find some function other than a power series in which to express the relation between E and r. The tractrix [equation (3)] seemed a good choice since it automatically fulfils the necessary conditions and has only two disposable parameters, a, b.

$$r = \frac{1}{b}\left[a \log\left(a + (a^2 - E^2)^{1/2}\right) - a \log E - (a^2 - E^2)^{1/2}\right] \tag{3}$$

Attempts to fit a pair of tractrices to the data on bond lengths and heats of formation proved awkward, however, owing to the cumbersome nature of the tractrix function. We therefore decided to combine the determination of the disposable parameters (a_C, b_C, a_H, b_H) in the tractrix equations for CC and CH bonds with the calculation of the sp^2–sp^2 C—C bond length outlined in Part I.[1] This procedure enabled us to

[18] R. S. Mulliken, C. A. Rieke and W. G. Brown, *J. Amer. Chem. Soc.* **63**, 40 (1941).
[19] G. Glockler, *J. Chem. Phys.* **21**, 1242, 1249 (1953); *Ibid.* **61**, 31 (1957).
[20] H. Feilchenfeld, *J. Chem. Phys.* **61**, 1133 (1957).

calculate a number of bond lengths which could be compared with experiment, and so provided a useful check on the general validity of our assumptions.

IV. *Calculation of the* C—C *bond energy–bond length relation*

In Part I[1] we outlined a technique for calculating the equilibrium bond lengths in benzene (r_b) and graphite (r_g) in terms of the following parameters:

r_e' E_e' (equilibrium bond length and equilibrium bond energy for the sp^2–sp^2 C—C single bond)

r_e'' E_e'' (corresponding values for C:C double bond)

k_e' k_e'' (force constants for single and double bonds between sp^2 carbon atoms at equilibrium bond length)

The force constants are either known (k_e'') or can be found by interpolation. The tractrix equations (3) provide relations between bond length and bond energy. One

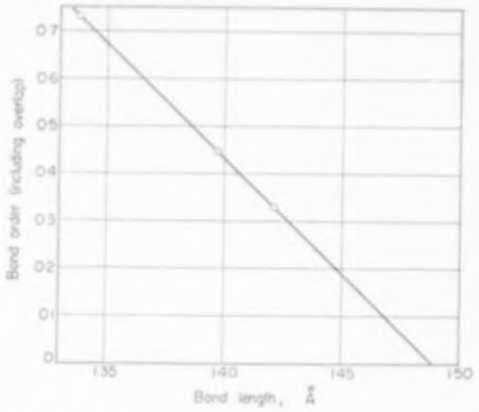

FIG. 3. The corrected plot of bond length vs. bond order.

difficulty arises here: the calculations are carried out with *equilibrium* bond lengths and bond energies, whereas the experimental values for bond lengths and bond energies refer to molecules in their vibrational ground states. These ground-state values (r_0, E_0) require correction; the correction to E_0 is simply equal to the zero point energy; the correction to r_0 is considered in Appendix 2.

In order to minimize the amount of experimental data used, and to check the validity of our conclusion (cf. Fig. 3) that the bond order–bond length plot is linear, we assumed in our calculation that this was the case. The only experimental data* we used were the following:

heat of formation and CC bond length in diamond.

heat of formation and CH bond lengths in methane and ethylene.

heat of formation of acetylene.

the CC force constants in ethane, ethylene and acetylene.

We were then able to calculate without any further assumptions the following sixteen quantities:

r_0', E_0' (the mean bond length and bond energy of the sp^2–sp^2 C—C bond in its vibrational ground state)

* The thermochemical data are referred to 0°K; see section V, p. 104.

r_e', E_e' (the corresponding equilibrium values)
r_0, E_0, r_e, E_e (corresponding values for the sp^3–sp^3 CC bond)
r_b, r_g (equilibrium bond lengths in benzene and graphite respectively)
r_0'' (mean C:C bond length in ethylene in its vibrational ground state)
r_e'' (corresponding equilibrium value)
a_C, b_C, a_H, b_H (constants in the tractrix equations)

Details of the calculation are given in Appendix 3.

Table 3 shows a comparison of the observed and calculated values for r_g, r_b and r_0''. The remarkable agreement strengthened our confidence in the conclusions we had reached and assumptions we had made in reaching them.

TABLE 3. COMPARISON OF CALCULATED AND OBSERVED BOND LENGTHS

CC bond in	Symbol	Bond length in Å	
		Calculated	Observed
benzene	r_b	1·397	1·397 ± 0·001
graphite	r_g	1·421	1·4211
ethylene	r''	1·338	1·333[15]
			1·337[16]
			1·339[17]

Table 4 compares three different theoretical estimates for r_0' with experimental values for the lengths of sp^2–sp^2 single bonds (Table 1). The agreement between these four values provides further evidence that no significant resonance shortening of the central bond occurs in molecules such as diphenyl or butadiene.

TABLE 4. ESTIMATES OF THE LENGTH (r_0') OF THE sp^2–sp^2 C—C BOND

Method	Length (Å)
r/s-character plot	1·486
r/bond order plot	1·489
benzene–graphite calculation	1·489
experiment	1·483, 1·492, 1·470[a]

[a] See Table 1.

Table 5 lists the values of the parameters a_C, b_C, a_H, b_H in the tractrix equations.

TABLE 5. PARAMETERS IN THE TRACTRIX EQUATIONS

Type of bond	a (kcal/mole)	b (kcal/mole Å)
CC	2919·8828	6116·1936
CH	4144·6424	13022·007

V. *Derivation of bond energies*

The values found in this way for the various C—C and CH bond energies were (in kcal/mole):

$$E_0 = 84{\cdot}56;\ E_0' = 94{\cdot}99;\ \epsilon_0 = 98{\cdot}19;\ \epsilon_0' = 100{\cdot}52 \qquad (4)$$

These values when substituted into equation (1) give an estimated value for the stabilization energy of butadiene at 0°K of 5·8 kcal/mole, compared with the experimental value (see Table 10, p. 109) of 8·6 kcal/mole. This suggests that at least the major part of the stabilization of butadiene can be ascribed to changes in bond energy with hybridization rather then to resonance.

A similar calculation can be carried out for semiconjugated hydrocarbons. The bond energy of the sp^3–sp^2 C—C bond can be estimated from its length (1·515 Å) using the tractrix equation; this (89·59 kcal/mole) leads in turn to an estimated value of 2·7 kcal/mole for the stabilization energy per sp^3–sp^2 C—C bond in semiconjugated systems, in good agreement with experiment (Table 10).

These results are gratifying in view of the extremely scanty thermochemical data used in calculating the bond energies; they suggest that our estimates of the variation in bond energy with hybridization for CC and CH bonds are not far from the truth. This in turn supports our suggestion that the theoretical interpretation of the thermochemistry of carbon compounds needs complete revision; the assumption that bond energies do not vary with hybridization is not even a passable first approximation.

One further difficulty remained, however, in our interpretation. It is known that the heats of formation of paraffins cannot be expressed accurately as sums of bond energies, and it is generally agreed[21] that the discrepancies are due to non-bonded interactions of some kind. Not wishing to commit ourselves to any specific interpretation of these interactions, we decided to allow for them empirically by absorbing them into the sp^3 CH bond energies. The value given in Table 4 refers to methane where there are no non-adjacent bonds; we found that the available data could be well interpreted by introducing just two empirical parameters, the CH bond energies in methyl, and in methylene or methine groups. No correction was needed for any of the other CC or CH bond energies; their values were estimated from the experimentally determined bond lengths by using the appropriate tractrix equations.

Table 6 lists the bond energies found in this way, together with the assumed bond lengths. Note that all our thermochemical calculations are for compounds in the gas phase at the absolute zero. The use of data corrected to 0°K avoids complications from specific heat differences and from conformational isomerism (cf. Section VI, p. 106); at 0°K each hydrocarbon will be in its most stable conformation.

Table 7 compares the observed heats of formation from atoms in the gas phase at 0°K of a number of hydrocarbons with those calculated from the bond energies in Table 6. The agreement is excellent for the paraffins and satisfactory for the semiconjugated olefines and acetylenes, especially in view of the fact that all but two of the bond energies were calculated from limited experimental data by a clear-cut theoretical method, rather than fitted to the available values for heats of formation; and in view of the fact that the experimental values are liable to errors of a few tenths of a kcal/mole. Table 7 suggests that one or two of the bond energies may be in error by small amounts; these will be discussed below. There seem to be marked deviations (~2 kcal/mole) for cycloparaffins and conjugated dienes and large deviations for the benzene derivatives.

[21] cf. J. R. Platt, *J. Chem. Phys.* **15**, 519 (1947); M. J. S. Dewar and R. Pettit, *J. Chem. Soc.* 1625 (1954); K. S. Pitzer, *J. Chem. Phys.* **23**, 1735 (1955); K. S. Pitzer and E. Catalano, *J. Amer. Chem. Soc.* **78**, 4844 (1956); L. S. Bartell, *J. Chem. Phys.* **32**, 827 (1960).

TABLE 6. BOND ENERGIES AND BOND LENGTHS[a]

Type of bond		Symbols used in text for length and bond energy	Bond length (Å)	Bond energy (kcal/mole) at 0°K.
C—C	sp^3–sp^3	r_0, E_0	1·544	84·56
	sp^3–sp^3	r_0°, E_0°	1·517[b]	89·59[b]
	sp^3–sp		1·459	100·74
	sp^2–sp^2	r_0', E_0'	1·479[c]	94·99[c]
	sp^2–sp		1·432	105·82
	sp–sp		1·379	119·75
C=C	sp^2–sp^2	r_0'', E_0''	1·338	130·44
	sp^2–sp		1·310[d]	138·25
	sp–sp		1·282[d]	146·71
C≡C	sp–sp		1·205	170·55
C—H	sp^3 (methane)		1·094	98·19
	sp^3 (primary)	ε_0	1·102	97·01
	sp^3 (sec, tert)	ε_1	?	96·30
	sp^2	ε'	1·086	100·52
	sp	ε''	1·059	109·46

[a] Values for bonds in their vibrational ground states (i.e. r_0, E_0).
[b] These values for r_0°, E_0° may need revision ; see Section VII.
[c] The values for r_0' may be too large and for E_0' too small; see Table 9.
[d] Bond lengths in ketene, allene, butatriene; see Costain and Stoicheff[7].

VI. *Conformational effects in cyclohexane*

The deviations in cyclohexane derivatives are probably a conformational effect, due to dipole–dipole repulsions between adjacent CH bonds. Repulsions of this kind should make the all-*trans* conformation (Fig. 4a) of a polymethylene chain the most stable, there being just two pairs of adjacent CH bonds. Cyclohexane, in its stable

FIG. 4. Conformations of CH_2 groups (a) in centre of polymethylene chain at 0°K; (b) in cyclohexane (chain form). Broken lines indicate interactions between adjacent CH dipoles.

chain form, has an all-*gauche* conformation (Fig. 4b) in which there are three pairs of adjacent CH bonds on neighbouring carbon atoms; the heat of formation per methylene group in cyclohexane should therefore be less than that for methylene in an open chain by the repulsion energy per pair of adjacent CH bonds.

Taking the value 0·4 *D* for the CH bond moment and assuming the dipoles localized at the midpoints of bonds, we find for the CH repulsion energy 0·3 kcal/mole. The heat of formation of cyclohexane should be less than that calculated from the bond energies in Table 6 by six times this amount, i.e. 1·8 kcal/mole; this is just the observed discrepancy (Table 7). An extension of this argument shows that the discrepancy should be the same for alkylcyclohexanes, as also seems to be the case.

TABLE 7. COMPARISON OF CALCULATED AND OBSERVED[22] HEATS OF FORMATION OF HYDROCARBONS IN THE GAS PHASE AT 0°K

Hydrocarbon	Heat of formation (kcal/mole)		
	Calculated	Observed	Difference
methane	392·7	392·7	(0)
ethane	666·6	666·8	−0·2
propane	943·8	943·3	0·5
n-butane	1220·9	1221·0	−0·1
n-pentane	1498·1	1498·1	(0)
n-hexane	1775·3	1775·3	(0)
i-butane	1223·1	1222·6	0·5
i-pentane	1500·2	1499·6	0·6
neopentane	1502·4	1502·1	0·3
cyclohexane	1663·0	1661·1	1·9
methylcyclohexane	1942·3	1940·9	1·4
1:4-dimethylcyclohexane	2221·6	2220·1	1·5
propene	812·6	812·1	0·5
1-butene	1089·8	1089·1	0·7
1-pentene	1366·9	1366·5	0·4
1:4-pentadiene	1235·8	1234·7	1·1
trans-2-butene	1092·7	1091·8	0·9
1:3-butadiene	959·0	961·1	−2·1
1:3-pentadiene	1239·1	1241·0	−1·9
propyne	671·8	671·3	0·5
1-butyne	948·9	948·1	0·8
2-butyne	954·1	952·7	1·4
benzene	1279·4	1307·4	−28·0
toluene	1559·5	1587·4	−27·9
p-xylene	1839·6	1867·4	−27·8

VII. *Heats of formation of semiconjugated hydrocarbons*

Not only do the calculated and observed heats of formation of semiconjugated olefines and acetylenes agree quite well (Table 7) but also the calculated values are consistently the higher. Therefore insofar as our calculations have any validity they imply that resonance stabilization (hyperconjugation) in such molecules is negligible.

The small deviations in the case of the olefines seems to be proportional to the number of sp^2–sp^3 bonds, and those in the acetylenes proportional to the number of of sp–sp^3 bonds. This suggests that the corresponding bond energies in Table 6 are too high, by about 0·5 and 0·7 kcal/mole respectively, corresponding to increases of 0·003 Å in each bond length. This is surprising; for several recent determinations (Table 8) of the sp^2–sp^3 C—C bond length suggest that the value listed in Table 6 is already too great.

The matter needs further investigation. The values in Table 8 seem to be consistently less than those reported from X-ray diffraction. Although X-ray methods are less precise than those based on spectroscopy of electron diffraction, they are also less subject to systematic errors. Spectroscopic methods are particularly difficult to apply to asymmetric molecules owing to the complications caused by centrifugal distortion

[22] Calculated from Rossini *et al.*, *Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds* Carnegie Press, 1953.

and anharmonicity of vibrations. It is perhaps significant that the bond length data for sp^2–sp^3 and sp–sp^2 bonds show far more scatter than those for sp–sp^3 or sp–sp bonds; bonds of the latter type appear in linear or symmetrical top molecules whose rotational spectra are much easier to interpret, whereas bonds of the former type have been studied only in unsymmetrical molecules. However it does seem likely on balance that the bond length listed in Table 6 for the sp^2–sp^3 bond is too great.

TABLE 8. RECENT DETERMINATIONS OF THE LENGTH OF THE sp^3–sp^2 C—C BOND

Compound	Length (Å)
CH_3COF	1·503 ± 0·003[a]
CH_3COCN	1·490 ± 0·01[b]
CH_3COOH	1·497 ± 0·01[c]
$(CH_3)_2C{:}CH_2$	1·506[14]

[a] L. Pierce and L. C. Krisher, *J. Chem. Phys.* **31**, 875 (1959).
[b] L. C. Krisher and E. D. Wilson, *J. Chem. Phys.* **31**, 882 (1959).
[c] W. J. Tabor, *J. Chem. Phys.* **27**, 974 (1959).

TABLE 9. VALUES OF E' AND CORRESPONDING RESONANCE ENERGY OF BUTADIENE FOR VARIOUS VALUES OF r'

r' (Å)	E' (kcal/mole)	Resonance energy (kcal/mole)
1·489	94·99	2·07
1·486	95·41	1·65
1·484	95·99	1·07
1·481	96·58	0·48
1·479	97·00	0·06

It is also possible that the value for the C—C bond length in hydrocarbons may be less than that in diamond; a recent spectroscopic study of ethane has given[23] a value 1·534 Å for the CC bond length.

VIII. *Conjugated dienes*

In the case of butadiene and 1:3-pentadiene the calculated heats of formation (Table 7) are less than those observed by about 2 kcal/mole; this difference could be ascribed to resonance stabilization. Note that the value for pentadiene is *less* than that for butadiene; here again there is no evidence for resonance stabilization due to hyperconjugation.

The value of 2 kcal/mole for the resonance energy may not be genuine. It depends on the bond energy (E') ascribed to the sp^2–sp^2 C—C bond, and this in turn depends on its length (r'). The values listed in Table 4 suggest that r' could have a value anywhere in the range 1·479–1·489 Å; Table 9 lists corresponding values of E' and of the derived resonance energy of butadiene, which can have any value between zero and 2 kcal/mole.

[23] H. C. Allen and E. K. Plyler, *J. Chem. Phys.* **31**, 1062 (1959).

It is evident that the resonance shortening of the sp^2–sp^2 bond in butadiene must be small; taking the maximum value for r' (1·489 Å), the shortening would be less than 0·01 Å—and this would have to correspond to a resonance stabilization of 2 kcal/mole. This seems rather unlikely. The data certainly suggest that r' does not appreciably exceed the measured length (1·483 Å) of the central bond in butadiene and that the resonance energy is less than 1 kcal/mole.

TABLE 10. HEATS OF HYDROGENATION OF HYDROCARBONS IN THE GAS PHASE AT 0°K, AND VARIOUS DERIVED QUANTITIES

Compound	Heat of hydrogenation[a]	*SE*[a]	*HE*[a]	*CE*[a]
ethylene	31·04	—	—	—
propene	27·95	3·09	2·93	0·15
1-butene	28·63	2·41	2·93	−0·52
1-pentene	28·36	2·68	2·93	−0·25
1:4-pentadiene	56·86	5·22	5·86	−0·64
trans-2-butene	25·91	5·13	5·86	−0·73
1:3-butadiene	53·45	8·63	6·24	2·39
1:3-pentadiene	50·62	11·46	9·17	2·29
benzene	44·01	49·11	18·72	30·39
toluene	43·80	49·32	19·52	29·80
p-xylene	43·06	50·06	20·32	29·74

[a] in kcal/mole for reaction in the gas phase at 0°K.

IX. *Heats of hydrogenation; stabilization energies*

Table 10 lists heats of hydrogenation in the gas phase at 0°K for several hydrocarbons, calculated from published data.[22] The third column gives corresponding stabilization energies. Note that the values for classical molecules correspond to a stabilization of about 2·7 kcal/mole per sp^2–sp^3 bond, and 8·6 kcal/mole per sp^2–sp^2 bond.

The equations given in Part I[1] for the contribution to *SE* due to such hybridization effects (a quantity we may term *hybridization energy*, *HE*) need modification for the effects of non-bonded interactions in the paraffinic reduction products (Section V). When these are taken into account as here by ascribing different bond energies ϵ_p, ϵ_s to primary, and to secondary or tertiary, CH bonds, the equation for *HE* in olefines becomes:

$$HE = m\{(E_0^* - E_0) - (\epsilon' - \epsilon_p)\} + n\{(E_0' - E_0) - 2(\epsilon' - \epsilon_p)\} + (2m + 4n - 3b)(\epsilon_p - \epsilon_s) \quad (7)$$

where m, n are respectively the numbers of sp^3–sp^2, and sp^2–sp^2 C—C bonds, and b is the number of unsaturated branches in the olefine (i.e. the number of groupings $R_1R_2C = C<$); for the other symbols see Table 6. The first two terms in equation (7) are those previously derived,[1] the last term is the correction for the difference between primary and secondary CH.

The fourth column of Table 10 lists *HE* values calculated in this way. The values for simple olefines are essentially identical with the *SE*'s, confirming that the thermochemical data provides no evidence for resonance; in the case of butadiene and 1:3-pentadiene, the difference between *SE* and *HE*—which could be ascribed to resonance

stabilization—is again about 2 kcal/mole, in agreement with the estimate from heats of formation (Table 7). This calculation of course also depends on the values ascribed to E', and hence to r'; if $r' < 1{\cdot}489$ Å, the difference between *SE* and *HE* would be less, vanishing if $r' = 1{\cdot}479$ Å [cf. Table 9 with equation (7)].

Even with the highest reasonable value (1·489 Å) for r', the resonance energy of butadiene is less than a quarter of the observed stabilization energy; and, as was pointed out in the previous section, the true value is probably less. This confirms our earlier[1] conclusion that resonance plays a minor role in the stabilization of classical conjugated hydrocarbons.

Table 11. Calculation of the resonance energy of benzene for extreme values of r'

	CE[a]	*SRE*[a]	*RE*[a]
from heat of formation:			
$r' = 1{\cdot}479$ Å	21·94	15·27	6·7
$r' = 1{\cdot}489$ Å	27·94	14·84	13·1
from heat of hydrogenation:			
$r' = 1{\cdot}479$ Å	23·98	15·27	8·7
$r' = 1{\cdot}489$ Å	29·98	14·84	15·1

[a] in kcal/mole.

X. *Benzene*

Benzene and its derivatives appear to have large resonance energies, whether these are estimated from heats of formation (Table 7) or from heats of hydrogenation (Table 8). The values in all cases are about 30 kcal/mole. The fact that the values for benzene, toluene, and *p*-xylene are the same indicates that hyperconjugation between the methyl groups and the ring leads to no significant additional stabilization.

These values are subject to correction for changes in the sp^2–sp^2 C—C bond energy (E'); if $r' = 1{\cdot}479$ Å, the apparent resonance energy of benzene would fall to 22 kcal/mole. Table 11 gives mean values for benzene, toluene, and *p*-xylene derived from heats of formation, and from heats of hydrogenation, for the highest and lowest values of E' listed in Table 9.

As was pointed out in Part I,[1] there is a further factor to be considered. The "resonance energies" listed in the first column of Table 11 represent the calculated differences in total energy between benzene and a classical cyclohexatriene with double bonds of length 1·338 Å, and single bonds of length 1·479 or 1·489 Å. But these differences in energy cannot be equated to the difference in π-electron energy between benzene and classical cyclohexatriene—which alone can properly be termed resonance energy (*RE*); the values in Table 11 also contain[1] a contribution due to the difference in σ-bond length, and consequently in σ-bond compression, between the two structures. The energy required to compress *three* single bonds to the lengths (1·338 Å) of the double bonds in cyclohexatriene is greater than that required to compress *six* such single bonds to the lengths (1·397 Å) of the bonds in benzene. This effect stabilizes benzene by a quantity which may be termed *σ-strain relief energy* (*SRE*), the values of which are listed in the second column of Table 11. The last column gives the true resonance energies, found by difference. The quantity in the first column (i.e. *SRE* +

RE) may be termed *conjugation energy* (*CE*); it is equal to the difference between the stabilization energy and hybridization energy.

Inspection of Table 11 shows that the true resonance energy of benzene probably lies in the range 5–15 kcal/mole. These values are much less than those commonly quoted and support our contention[1] that only about a quarter of the stabilization of benzene is due to resonance.

Current estimates of the resonance energy of benzene have neglected the effect of hybridization, and most of them have also neglected σ-bond compression.

TABLE 12. CALCULATION OF BOND LENGTHS AND ENERGY FOR BUTADIENE

Structure	Equilibrium bond lengths (Å)		Total CC bond energy at equilibrium (kcal/mole)
	1:2 Bond	2:3 Bond	
classical	1·334	1·485	362·49
actual	1·336	1·479	361·80
(difference)	0·002	−0·006	−0·69

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XI. *Calculation of bond lengths in butadiene*

When we began this investigation our object was to calculate bond lengths in conjugated systems allowing for the effect of σ-bond compression. Further investigation has shown that the method we at first proposed[1,3] for doing this suffers from a curious defect (Appendix 4). We have, however, been able to develop a technique for calculating bond lengths by directly minimizing the total energy of the molecule with respect to variations in the lengths of the individual bonds (Appendix 4) and we have applied this technique to butadiene. The results of this calculation are given in Table 12. The first row gives equilibrium bond lengths and total energy for a classical structure with localized single and double bonds. The second row gives corresponding values for the actual molecule. The third row shows the differences in bond lengths and energy due to resonance interactions.

Note that the changes in bond length are very small and the calculated resonance energy *negative*. This certainly supports our conclusion that resonance effects in butadiene are insignificant, particularly since we used a simple MO method which is known to overestimate resonance in butadiene.

It should be pointed out that the resonance effects found by us are much less than those given by apparently more precise methods. We think that our calculation is in fact the more reliable in spite of its simplicity since, unlike other investigators, we proceeded by minimizing the total energy of the molecule rather than relying on relations between bond order and bond length. Moreover the bond order–bond length relation used by other workers is probably incorrect. A further difficulty arises in the case of one-electron resonance integrals. These cannot be evaluated theoretically, and we feel that our empirical method for estimating them is better than the methods used by other authors (e.g. the assumption that resonance integrals are proportional to overlap). As will be seen presently, current methods must in any case overestimate resonance effects in butadiene, due to their neglect of electron correlation; we may have made some tacit allowance for this through our empirically determined resonance integrals.

XII. *Electron correlation;* the importance of vertical correlation*

In Part I[1] we drew attention to the effects of electron correlation in conjugated molecules and we concluded that the relatively high bond order ascribed by current treatments[6] to the central bond in butadiene is an artefact of an illegitimate assumption inherent in all of them. Since the argument has been misunderstood, we repeat it here in a clearer and more definite form.

The coulomb repulsion energy between two electrons occupying orbitals in a given atom or molecule can be calculated by standard methods. If we calculate in

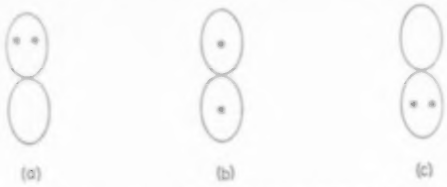

FIG. 5. Configurations of two electrons occupying a *p*-AO.

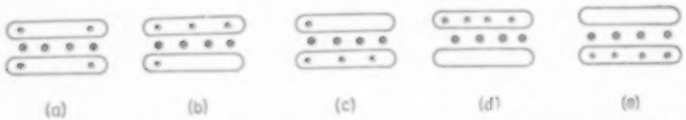

FIG. 6. Configurations of the π-electrons in butadiene; the dots denote the carbon nuclei.

this way the repulsion energy for a pair of electrons occupying the same $2p$-AO of a carbon atom we obtain a value which is much too large. The reason for this discrepancy is well known; it is due to the neglect of electron correlation in simple orbital calculations.

We can distinguish three configurations for the pair of electrons (Fig. 5).† In (a), (c) the electrons occupy the same lobe of the *p*-AO, in (b) different lobes.

In a simple orbital treatment each electron is supposed to move independently of the other, so that the chance of finding it in a given lobe is always 1/2. The weights of the three configurations would then be in the statistical ratio, (a):(b):(c) = 1:2:1. Configuration (b) is, however, favoured by the fact that in it the mean distance between the electrons is greater and the repulsion between them correspondingly less; the mean coulomb repulsion is therefore less than that calculated on the basis of simple orbital theory. In other words the electrons reduce their mutual repulsion by correlating their motions, so that most of the time they occupy different lobes of the *p*-AO.

A similar situation arises in the case of butadiene, when four electrons occupy in pairs two four-centre π-MO's. Here the electrons can keep apart in two ways; either by occupying different lobes of the π-MO, or by spreading themselves out along a given lobe. We shall refer to correlation of the first kind as *vertical correlation*, that of the second kind as *horizontal correlation*.

Fig. 6 indicates the main types of configuration: in (a), two electrons occupy each

* In this paper we again use[1] the term "electron correlation" in its naive sense, to imply the tendency of electrons in a molecule to correlate their motions, throughout the effects both of the Pauli principle and of coulomb repulsion.

† In order to make the argument clearer, the *p*-AO has been represented in the form corresponding to a real wave function.

π-lobe, in (b), (c) three electrons occupy one π-lobe, and in (d), (e) all four electrons are in the same π-lobe.

Simple orbital theory assumes that the probability of finding a given electron in a given π-lobe is always 1/2, independent of the positions of the other electrons; in this case the weights of the configurations would be in the ratio (a):(b):(c):(d):(e) = 6:4:4:1:1. However the mutual repulsion of the electrons will favour configuration (a) since in it the electrons are less bunched together; the weight of configuration (a) will therefore be greater than that implied by simple orbital theory.

This favouring of configuration (a), vertical correlation has the effect of reducing the overall coulombic repulsion between the π-electrons, and so reducing the total energy of the molecule. This is exactly analogous to the effect of correlation in atoms (cf. Fig. 5) and it can be taken into account to some extent by empirical adjustment of interelectronic repulsion integrals.[23,24] There is, however, a second much more serious consequence of electron correlation which cannot be approximated in this way.

In an atom the mean electron distribution is determined by symmetry; correlation cannot alter this mean electron distribution—it affects the instantaneous motions of electrons, not their mean positions averaged over a long period. This is not true for molecules. Consider the case of butadiene. The electrons in a given π-lobe will tend to spread out along it in response to their mutual repulsion (horizontal correlation). In the configuration of Fig. 6(a), each pair of electrons will tend to occupy the terminal bonds, due to their mutual repulsion. Configuration 6(a) therefore corresponds to high π-electron density in the terminal bonds, and low π-electron density in the central bond. When on the other hand three or four electrons occupy the same π-lobe [Fig. 6 (b)–(e)], the extra electron or electrons will tend to be forced into the central bond. Neglect of vertical correlation leads one to overestimate the importance of these latter configurations and so to overestimate the average electron density in the central bond.

Now *not one* of the existing treatments of π-electron systems takes this effect of vertical correlation into account. Adjustment of integrals[24] compensates to some extent for the effect of vertical correlation on the energy, but not for its effect on the wave function—and consequently on the electron distribution. Inclusion of configuration interaction in its conventional form[25] allows only for the effect of horizontal correlation. There can therefore be no doubt that all current treatments of butadiene *must* overestimate the electron density in the central bond of butadiene and the consequent resonance shortening; and there is at present no way of estimating the magnitude of this error.

Mulliken[6] based much of his criticism of our work on the results of such calculations; the argument given above shows that no valid conclusions can be drawn from such calculations and so refutes his criticisms.

An extension[1] of this argument suggests that current methods should always overestimate the effect of resonance in classical unsaturated molecules, and that these may well conform closely both in structure and in energy to the pattern predicted for a configuration with essentially localized single and double bonds. In such

[24] W. E. Moffitt, *Proc. Roy. Soc.* A **210**, 224, 245 (1951); R. Pariser and R. G. Parr, *J. Chem. Phys.* **21**, 466, 767 (1953).
[25] D. P. Craig, *Proc. Roy. Soc.* A **200**, 474 (1950).

molecules vertical correlation tends to share them equally between the two π-lobes, and horizontal correlation then spreads out the electrons in each π-lobe so that they tend to be concentrated in alternate bonds. But such a set of alternate bonds in a conjugated system must be the set written as double in one classical structure; electron correlation therefore tends to concentrate the electrons in each π-lobe into the bonds written as double in a classical structure for the molecule. If there is only one such structure, the π-electrons tend to be concentrated in pairs in the double bonds; the electron distribution will then conform more closely to that of a single classical structure than one would expect from current theoretical treatments in which electron correlation is neglected.

The situation is entirely different in non-classical molecules for which two or more classical structures can be written, i.e. aromatic molecules and mesomeric ions and radicals such as allyl. Here the two sets of π-electrons have a choice of classical structures and there is no question of their being localized in definite bonds. Consequently vertical correlation will not affect the smearing of electrons over the whole conjugated system; vertical correlation should affect the energy of a non-classical molecule but should not much affect the electron distribution in it. In this case conventional treatments have much more chance of success, particularly if allowance is made for the effect of vertical correlation on the energy.[26]

XIII. *The significance of classical structures*

Our argument implies that vertical correlation of the π-electrons in a conjugated system favours configurations in which the electrons are evenly distributed between the two π-lobes, and that horizontal correlation then tends to concentrate each such set of electrons into the bonds written as double in a classical structure for the conjugated system. According to this view classical structures take on a new significance; they represent instantaneous electron distributions favoured by electron correlation. This suggests that a special weight should be given to such structures in a resonance interpretation of conjugated systems; and that in such an interpretation the individual structures have a much more profound significance than is ascribed to the canonical structures of the VB theory.

This is interesting; for it is well known that simple resonance theory, in which excited structures are neglected, gives a very good account of chemical behaviour, although detailed calculation[26] has shown that excited canonical forms can be of dominant importance in the VB wave functions of aromatic molecules. We ascribe this apparent anomaly to the neglect of vertical correlation in VB theory.

The same conclusion, that the inclusion of excited structures in resonance theory is wrong in principle has also been reached by a different line of reasoning,[27] not incompatible with that given here.

Our argument does, however, suggest that resonance structures other than classical ones should be important. Each classical structure represents a preferred correlation pattern for the set of electrons occupying a given π-lobe. If both sets of π-electrons conform to the same classical structure, the resulting configuration as a whole will conform to the classical formulation in which each line represents a pair of electrons concentrated in the region between two nuclei. If, however, there are two or more

[26] A. Pullman and B. Pullman, *Experientia* **2A**, 364 (1946).
[27] M. J. S. Dewar and H. C. Longuet-Higgins, *Proc. Roy. Soc.* A **214**, 482 (1952).

possible classical structures, the two sets of π-electrons may adapt different distribution patterns, giving rise to a quasi-classical configuration in which certain "π-bonds" contain single electrons. Thus in the case of benzene, if both sets of electrons match up, we have the two Kekulé structures, Fig. 7 (a), (b); but if the two sets of electrons conform to different classical structures, we have the quasi-classical structures (c), (d) with one π-electron per CC bond.

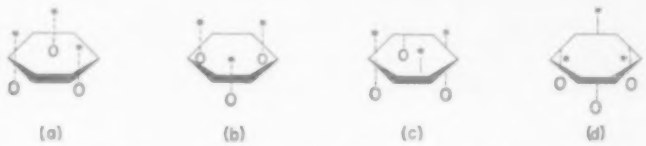

FIG. 7. Favoured configurations for π-electrons in benzene.

The structures (c), (d) correspond to the structure for benzene proposed by Thomson[28] with three electron bonds; they may be described as *Thomson structures*. Our argument implies that benzene can be represented as a hybrid of two Kekulé structures and to Thomson structures; the Thomson structures can be represented conventionally by writing broken lines for one electron π-bonds; Naphthalene pro-

vides a further illustration; here there are three classical structures; combination of these in pairs (corresponding to the two sets of π-electrons exhibiting different correlation patterns) gives three classical (Kekulé) and three semi-classical (Thomson) configurations; i.e.

In the simple MO treatment, effects of electron repulsion are included in the empirical resonance integrals. If these are evaluated, as in our treatment, from ethylene, they will correspond to the electron repulsion between pairs of electrons occupying the same C:C bond (i.e. a classical or Kekulé configuration). The electron repulsion in the staggered semi-classical Thomson configuration should be less than this; our treatment of benzene should therefore give too high a value for the energy, the difference being due to the contributions of the two lower-energy Thomson structures to the ground state. This certainly seems to be the case. The conjugation energy calculated for benzene (Section V) was only 1·9 kcal/mole compared with the experimental value (Table 11) of 20–30 kcal/mole. A rough calculation shows that this difference is of the same order of magnitude as the difference on electron repulsion energy between Kekulé and Thomson structures.

It is noteworthy that our method gave such a good value for the bond length in benzene (Table 3) although the value for the energy was much too high. This would

[28] J. J. Thomson, *Phil. Mag.* **27**, 784 (1914).

not be surprising if our explanation for the discrepancy is correct since the difference in electron repulsion between the Kekulé and Thomson structures is insensitive to bond length. Only the derivative of this difference with respect to bond length would enter our calculation, and this should be small.

XIV. *Possible methods for including vertical correlation*

Vertical correlation can be included in calculations of conventional type in one of two ways. Either one can use weighting factors involving the interelectronic distances directly (cf. the Hylleraas treatment of helium) or one can use a configuration interaction treatment in which vertical correlation is taken into account in the individual configurations, using configurations with varying numbers of electrons in the two π-lobes.

A treatment of the first kind had been described by Kolos[29] but so far he has applied it only to molecules such as ethylene or benzene where the π-MO's are determined by symmetry; any extension to more complex molecules would be very difficult. The second type of treatment has not yet been carried out.

There is, however, a third approach, suggested recently by Dr. C. E. Wulfman and one of us[30] and based on the relation between the MO and VB approximations.

The simple MO method is known to overestimate the importance of ionic structures, due to its neglect of electron correlation. An alternative approach is to make the opposite assumption, that electron correlation is so extreme that the chance of finding both electrons in a bond simultaneously on the same terminal atom is zero—in other words that ionic structures can be neglected. This leads to the VB approximation.

We can make the same simplifying assumption in the case of conjugated systems. We can assume that vertical correlation is so extreme that only configurations with equal numbers of electrons on either side of the nodal plane are important. A treatment of this kind was applied[30] to simple polyenes, the FEMO approximation being used for the electrons in each π-lobe; extension of this work seems most desirable since a comparison with the results of conventional treatments (in which vertical correlation is ignored) would indicate the maximum effect that vertical correlation can have.

It should be added that the experimental value for the mutual repulsion between two electrons occupying a $2p$-AO of carbon corresponds[30] to complete correlation implying that the chance of finding both electrons in the same lobe of the AO is small. This calculation suggests that the completely correlated model for π-electron systems may correspond closely to reality.

XV. *Significance of hybridization*

A number of authors have considered the possibility of a continuous transition between pure p and pure s bonds, the division of carbon bonds into sp^3, sp^2 and sp types being arbitrary. This view has been recently stressed by Mulliken[6]; if it were correct, our distinction of bonds into distinct hybridization types would lose much of its significance.

This argument is tacitly based on the assumption that σ-bond orbitals are linear, so that the valence orbital of carbon must point along the bond axis. It ignores the

[29] W. Kolos, *Acta Phys. Polonica* **16**, 257, 267, 299 (1957).
[30] M. J. S. Dewar and C. E. Wulfman, *J. Chem. Phys.* **29**, 158 (1958).

possibility of non-collinear overlap giving rise to bent bonds ("banana bonds"). Coulson and Moffitt[31] have shown that the structure of cyclopropane can be very well interpreted in terms of such bent bonds; and the experimental evidence concerning bond lengths, etc., provides no support for the continuous transition of bond properties with bond angles that would be expected if hybridization changed in conformity with bond angles.

Electron correlation should favour symmetrical distributions of the valence electrons of carbon, particularly near the nuclei; this in turn will favour bent bonds in cases where mutual repulsion or geometrical constraint forms the adjacent atoms out of the most symmetrical arrangement. Thus in the case of quadricovalent carbon, the four bond orbitals should set out symmetrically from the nucleus; this corresponds to (possibly non-collinear) overlap of four ligand orbitals with sp^3 hybrid orbitals of carbon. The idea of continuous variation of hybridization parameters probably implies an underestimate of the effects of electron correlation.

The significance of hybridization is in any case uncertain. The properties of a molecule depend only on the overall electron distribution, as expressed in the density matrix. Orbitals, hybridization, etc. are purely artificial concepts made necessary by our inability to calculate the electron distribution accurately or more directly. In this sense the correlations we have established between bond properties and co-ordination number may have a deeper significance than our interpretation would suggest; we have, however, preferred to formulate it in terms of hybridization for lack of a better theoretical model.

Appendix 1

Attempted calculation of bond energies. If the heats of formation of hydrocarbons can be expressed in terms of bond energies, then for a given hydrocarbon;

$$\sum_i n_i E_i + \sum_j n_j \epsilon_j = \mathrm{H} \tag{8}$$

where E_i is the bond energy of a given type of CC bond and n_i the number of such bonds, ϵ_j and n_j the corresponding quantities for CH bonds, and H the heat of formation.

If a number of hydrocarbons are considered, the set of equations (8) form a set of simultaneous equations for the bond energies. These can be written in the form

$$\mathbf{A} \cdot \mathbf{E} = \mathbf{H} \tag{9}$$

where **E** is the vector of bond energies, **H** the vector of heats of formation, and **A** the matrix of bonds of various types.

If we take a set of compounds whose heats of formation are known, **A** and **H** are known; equation (9) should then give the bond energies for bonds of various types. Unfortunately **A** proves to be a degenerate matrix; attempts to reduce the degeneracy of **A** sufficiently to solve equation (9) proved fruitless. Moreover random errors in the experimental values for heats of formation introduced enough "noise" to make the set of equations self-inconsistent.

[31] C. A. Coulson and W. E. Moffitt, *Phil. Mag.* **40**, 1 (1949).

Appendix 2

Correction of bond lengths for vibrational anharmonicity. If the vibration of a bond is anharmonic, the mean length (r_0) will differ from the equilibrium length (r_e). The relation between r_0 and r_e can be derived[32] but it is very cumbersome. Since the corrections in our case are small, we made the simplifying assumption that r_0 can be equated to the mean of the extreme bond lengths for a classical oscillator. Using the Morse potential, this leads to the expression

$$r_0 - r_e = -\left(\frac{2D_0 + hV_0}{k}\right)^{1/2} ln\left[1 - hV_0(2D_0 + hV_0)^{-1}\right] \tag{10}$$

where D_0 is the ground state bond energy, V_0 the ground state vibration frequency, and k the force constant.

TABLE 13. THE FORCE CONSTANT–BOND LENGTH RELATION

Compound	Equilibrium bond length	Force constant
ethane	1·540	4·57
ethylene	1·334	10·90
acetylene	1·205	15·48

$k = -46{\cdot}978r_e^{-2} + 194{\cdot}813r_e^{-4} - 136{\cdot}486r_e^{-6}$
bond lengths in Å, force constants in millidyne/Å

The corrections calculated from equation (10) for CC bonds are small (ethane, 0·0044 Å; ethylene, 0·0036 Å. acetylene, 0·0032 Å); the corrections for CH bonds are somewhat larger. Our crude method must overestimate the corrections, but the errors certainly cannot be important for the present purpose.

Appendix 3

The benzene–graphite calculation. The condition for equilibrium in benzene can be written

$$\frac{\partial E}{\partial r} = \frac{\partial E\sigma}{\partial r} + \frac{\partial E\pi}{\partial r} = 0 \tag{11}$$

where E is the total energy, E_σ, E_π the energies of the σ- and π-electrons, and r the bond length. The first term can be expressed in terms of the equilibrium force constant (k_e') for the sp^2–sp^2 C—C bond, from which together with its equilibrium length (r_e') one can calculate the Morse function parameters. The second term can be calculated by the method indicated in Part I,[1] using the simple LCAO method with inclusion of overlap; the values taken for the overlap integrals were those calculated from Hartree–Fock AO's. A similar equation can be written for the condition for equilibrium in graphite.

In order to estimate k_e', we assumed a relation between force constant and bond length of the form

$$k = ar^{-2} + br^{-4} + cr^{-6} \tag{12}$$

The constants a, b, c were found by fitting the force constants for ethane, ethylene, and acetylene; the data used and values found are listed in Table 13.

[32] cf. G. Herzberg, *Spectra of Diatomic Molecules*. Van Nostrand, New York (1950).

Sixteen quantities have to be determined (Section VI); viz. r_0', E_0', r_e', E_e', r_0 E_0, r_e, E_e, r_b, r_g, r_0'', r_e'', a_C, b_C, a_H, b_H. The equations available are:

equation (8) applied to r, r', r'' (three relations)
equation (4) applied to (r, E), (r', E'), (r'', E'') (three relations)
equation (9) applied to benzene and graphite (two relations)
equation (4) applied to diamond and methane (two relations)
equation for zero point energy, applied to find ($E_0 - E_e$) and ($E_0 - E_e'$) (two relations) heats of formation of ethylene and acetylene, expressed as sums of bond energies (two relations)
condition that the plot of bond order vs. r should be linear for four cases (ethylene, benzene, graphite, and pure sp^2–sp^2 single bond) (two relations).

There are therefore sixteen relations available, sufficient to determine the sixteen unknowns in terms of the experimental quantities listed in Section VI. The calculation was complicated by the fact that the computer available to us (a HEC 2M) had a limited store (1024 words); this made it impossible to put the whole problem on the machine. A solution was reached by varying E' until the equations became self-consistent. Full details of the calculation, which took 200 hours of machine time, are given in a thesis by one of us.[33]

Appendix 4

Calculation of bond lengths. In our previous papers[1,3] we proposed the following method for calculating bond lengths in conjugated systems.

The total energy (E) of the CC bonds in a conjugated system may be written

$$E = nE_0' + \sum C_{rs} + E_\pi \tag{13}$$

where n is the number of CC bonds and E_0' the corresponding σ-bond energy, C_{rs} is the energy required to compress the σ-bond between atoms r, s to the length it has in the conjugated system, and E_π is the total π-bond energy. In simple MO theory,

$$E_\pi = \sum_r q_r \alpha_r + 2 \sum_{r<s} \sum p_{rs} \beta_{rs} \tag{14}$$

where q_r, α_r are the change density at, and coulomb integral of, atom r, and p_{rs}, β_{rs} are the bond order and resonance integral of the bond between atoms r, s. In the MO treatment E_π is found by minimizing it with respect to the AO coefficients.

Combining equations (13) and (14),

$$E = nE_0' + \sum_r q_r \alpha_r + 2 \sum_r \sum_s p_{rs} \beta'_{rs} \tag{15}$$

where

$$\beta'_{rs} = \beta_{rs} + \frac{C_{rs}}{2p_{rs}} \tag{16}$$

Since equations (14) and (15) are similar in form, it would appear that a standard MO calculation, with β replaced by β', should give the total energy (including σ-bond compression) rather than π-energy. The replacement seems valid, since β, c, and p are all one-valued functions of bond length in molecules in equilibrium; β' should also be a one valued function of bond length.

[33] H. N. Schmeising, Ph.D. Thesis, London (1959).

In order to calculate E, an iterative procedure must be used. Values for the bond lengths are assumed; β_{rs}, c_{rs}, p_{rs}, and hence β'_{rs} are calculated for each bond; solution of the appropriate secular equations gives the orbital coefficients from which bond orders are calculated; and from these together with the p/r relation a new set of bond lengths are calculated. The cycle is repeated until the bond lengths become self-consistent.

The trouble with this idea is that p_{rs} does not have the same meaning in equations (15) and (16). In equation (15), p_{rs} is a bond order found from orbital coefficients; in equation (16) p_{rs} is found from the assumed bond lengths using the p/r relation. If the molecule were in its equilibrium state, the p's would be identical; but in the minimization procedure there is the danger of arriving at a false solution. This happened when we tried to apply the method to butadiene.

The difficulty might have been overcome, had not the following alternative and better based procedure made it superfluous. The problem is to minimize the total energy of butadiene with respect to simultaneous variation in two parameters (lengths of the 1:2 and 2:3 bonds). As Mr. F. Beck* pointed out to one of us, the problem can be solved by fitting parabolas to the energy surface and finding the total minimum of these. It can be shown that if x_0 is an approximation to the minimum of a two-dimensional curve $f(x)$, then a second approximation x'_0 is given by

$$x'_0 = x_0 - d(f_+ - f_-)/2(f_+ + f_- - 2f) \tag{17}$$

where d is a suitable increment, and f_+, f_- the values of $f(x)$ for $x = x_0 - d$.

If d is kept constant, then successive applications of equation (17) may not lead to a solution, since it may be that at some stage f_+, f_- become equal. This difficulty cannot occur if d is halved after each iteration.

Equation (17) can be applied for any number of variables provided the initial approximations are sufficiently good. A proof of the relation, and further discussion, will be found in a thesis[33] by one of us.

In applying the method to butadiene one needs to know β, s, and c as functions of bond length. The values of s, the overlap integral, were taken from tables,[34] calculated for Hartree–Fock orbitals. The values of β were found by the modified Lennard-Jones method described previously.[1] The compression energy was found from a Morse function.

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* Research Laboratories, General Electric, England.

[34] R. S. Mulliken, *J. Chem. Phys.* **19**, 900 (1951).

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MOLECULAR ORBITAL CALCULATIONS ON SOME NON-CLASSICAL AROMATICS

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Abstract—Calculations by the Hückel Molecular Orbital method have been made on ten non-classical aromatics, most of them non-alternant. Considerable resonance stabilization is predicted for all the systems studied. Except for charge distribution in the non-alternants, the calculated properties are mostly similar to those of normal benzenoid aromatics. The application to our systems of Craig's rules for predicting aromaticity is discussed.

THE simple Hückel Molecular Orbital Theory[2] has been used to calculate the properties of some non-benzenoid aromatic systems. In this procedure overlap is neglected, all coulomb integrals are considered equal, and all resonance integrals between adjacent carbons are considered equal. Calculations were carried out on an I.B.M. 650 computer, using a standard matrix-diagonalization program.[3]

The compounds considered are shown in Fig. 1, which also gives bond orders, free valences and charge densities (in parentheses following the free valences).[4] The charge densities of the alternant hydrocarbons II and V are unity at all positions. The values for the odd system I refer to the cation. Delocalization energies for I–X are given in Table 1.

For purposes of discussion, the results fall logically into three groups: (1) I, (2) II, V and (3) III, IV, VI–X. Of these substances, only III and IV are known.[5]

The cation I has the same number of π-electron centers as the tropylium ion and a slightly lower delocalization energy.[6] Unlike tropylium ion, I has a lowest unoccupied molecular orbital which is non-bonding, so the radical and anion from I should have the same delocalization energy as the cation (neglecting interelectronic repulsion). The electron deficiency of the cation is much greater in the four- than in the five-membered ring.

The cyclo-octatetraene derivatives II and V show no particularly unusual features. Delocalization energies per π-electron run somewhat less than those of benzenoid aromatics of comparable size (naphthalene is $0{\cdot}37\beta$ per π-electron). Our calculations do not, of course, consider bond-angle strains which could counterbalance the resonance stabilization of the planar system. II, at least, might be better than cyclo-octatetraene in this respect, since the fused four-member ring should help to flatten out the eight-member ring.

[1] To whom requests for reprints should be directed.
[2] [a] E. Hückel, *Z. Physik.* **70**, 240 (1931); [b] C. A. Coulson, *Valence* Chap. IX. Oxford University Press, London (1952); [c] H. Eyring, J. Walter and G. E. Kimball, *Quantum Chemistry* Chap. XIII. John Wiley, New York (1944).
[3] We thank the University of Rochester Computing Center for donating the time on the computer.
[4] These quantities were calculated from the coefficients of the atomic orbitals as described.[2b]
[5] K. Hafner and J. Schneider, *Liebigs Ann.* **624**, 37 (1959) have prepared dimethyl-substituted derivatives of III and IV, but not the parent hydrocarbons.
[6] J. D. Roberts, A. Streitwieser, Jr. and C. M. Regan, *J. Amer. Chem. Soc.* **74**, 4579 (1952) report $2{\cdot}99\beta$ for tropylium ion.

8A—(4 pp.)

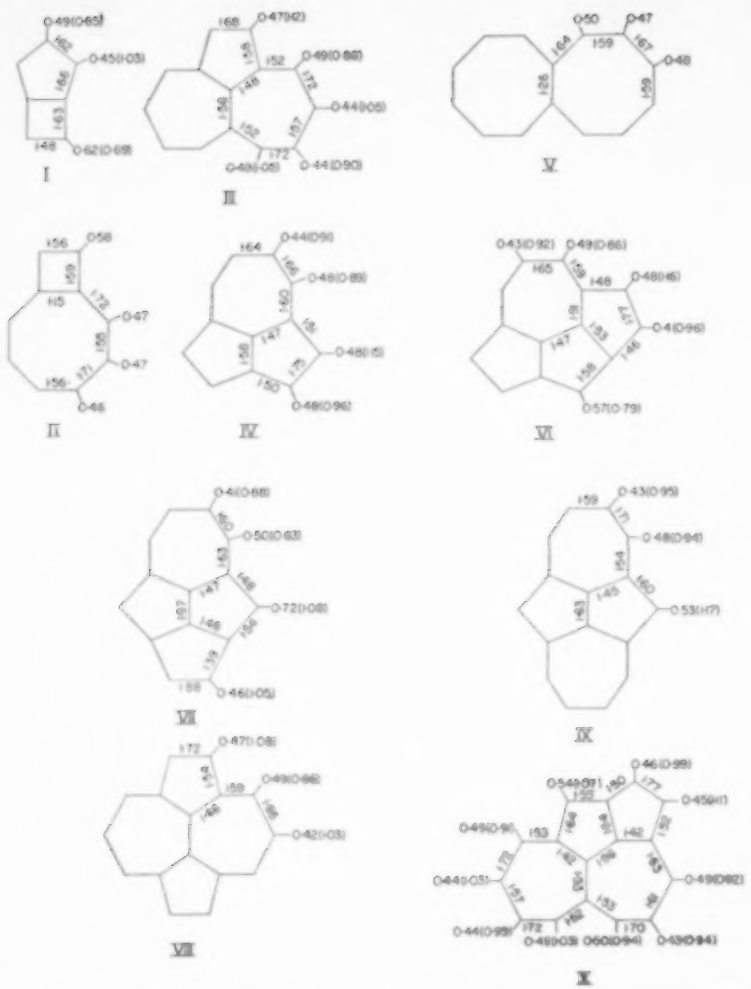


FIG. 1. Properties of some non-classical aromatics as calculated by the molecular orbital method. Numbers along the bonds are bond orders. Numbers at lines to ring positions are free valences. The numbers in parenthesis following free valences are charge densities.

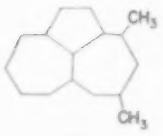
Of the remaining compounds none is known, but Hafner[5] has prepared the dimethyl derivatives XI and XII, of III and IV, respectively. Within the limitations of our approximations, the methyl groups should not significantly affect our conclusions. Both III and IV have delocalization energies comparable to those of the benzenoid aromatics and none of the other calculated properties (including the distribution of energy levels),[7] leads one to expect any pronounced differences between the two. Hafner[5], however, reports that XI behaves as a normal aromatic, forming a trinitrobenzene complex and giving electrophilic substitution reactions (though the Vilsmeier formylation with dimethyl formamide and $POCl_3$ in benzene is the only one actually

[7] After completion of our work we learned that Professor A. Streitwieser, Jr. has performed more complete calculations on III and IV, including localization energies for substitution reactions. His results will be published separately.

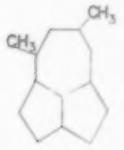
TABLE 1. DELOCALIZATION ENERGIES OF SOME NON-CLASSICAL AROMATICS

Compound[a]	Total DE[b]	DE per π-electron[b]
I	2·91	0·42
II	2·84	0·28
III	4·91	0·35
IV	4·37	0·36
V	4·10	0·29
VI	5·28	0·38
VII	5·13	0·37
VIII	6·04	0·38
IX	6·03	0·38
X	5·94	0·37

[a] See Fig. 1 for structures.
[b] In units of the resonance integral β (ca. 18 kcal/mole).



XI



XII

described). It also is recoverable from a solution in 50 per cent sulfuric acid. In contrast, XII gave no trinitrobenzene adduct and polymerized with acids and on heating so that no electrophilic substitutions could be performed. In defense of the theory one might point out that these differences are not necessarily consequences of differences in the π-electron systems of the isolated molecules and may arise from other factors such as bond-angle strain.

The remaining molecules, VI–X, are derived from III and IV by fusion of additional rings and mostly resemble III and IV in calculated properties. The delocalization energies per π-electron are also similar to those of benzenoid aromatics (compare with $0{\cdot}37\beta$ for naphthalene, $0{\cdot}38\beta$ for anthracene and $0{\cdot}41\beta$ for pyrene). Highest bond orders in most cases are in five-member rings, but the bonds that are common to five- and seven-member rings tend to have low bond orders. A point of particular interest is that the lowest unoccupied orbital of VII is non-bonding, while for the other compounds of this group it is antibonding ($-0{\cdot}20\beta$ to $-0{\cdot}44\beta$). One would thus expect VII to reduce to the radical-anion with unusual ease.

The charge densities follow the same patterns as in azulene. Negative charge concentrates in the 5-member rings and is highest on positions adjacent to a 7-member ring. The 7-member rings are electron deficient, usually having their lowest charge densities in positions next to a 5-member ring. One would expect considerable regularity in the substitution reactions of III–IV and VI–X, since electrophilic attack should occur at the position of highest and nucleophilic attack at the position of lowest charge density. Calculation of localization energies[8] would provide a check of these predictions, but the extra labor was not considered worthwhile in a preliminary survey dealing with mostly unknown molecules.

[8] G. W. Wheland, *J. Amer. Chem. Soc.* **64**, 900 (1942); R. D. Brown, *Quart. Rev.* **6**, 63 (1952).

The free valences, usually taken as measures of reactivity toward radicals, show considerably less consistency than the charge densities. In two compounds, VII and IX, the maximum free valence is at the same position as the maximum charge density. In all except VIII and X, the maximum free valence is in a 5-member ring. Free valences of one or more other positions of III, IV and X are quite close to the figure for the maximum position. For comparison, most normal benzenoid aromatics have free valences of 0·40–0·45, though the 9-position of anthracene has a free valence of 0·52. Overall, the predictions on radical attack are more ambiguous and probably less reliable than the predictions on electrophilic attack.

Whether more sophisticated approaches than simple molecular orbital theory would predict aromaticity for the compounds examined here is a point of some interest. An approach that is particularly easy to apply has been developed by Craig[9]. His arguments are based on the symmetry properties of the valence-bond ground states. Of our molecules, I, II and X do not possess sufficient symmetry for the method to be used. V is clearly aromatic. The remaining (and most interesting) cases, III, IV, VI, VII, VIII and IX, present problems of application.

XIII

XIV

These problems can be illustrated with III. The valence-bond structure XIII fits Craig's symmetry criterion for aromaticity, but the structure XIV does not. Dr. Craig believes that this indicates little stabilization by interaction of XIII and XIV, and consequently little aromaticity.[10] It is clear that from the valence-bond viewpoint all of these molecules are in some sense abnormal.[10] There is not yet adequate experimental evidence on this interesting extension of Craig's rules. Syntheses of VI–IX would certainly provide valuable information on the reliability of these symmetry arguments as well as the suitability of simple molecular orbital theory for treating non-alternant systems.

[9] D. P. Craig, *J. Chem. Soc.* 3175 (1951).
[10] D. P. Craig. Private communication.

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MOLECULAR DEFORMATION IN CYCLOÖCTADECANONAENE

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Abstract—Calculations are reported which show that the large cyclic polyene $C_{18}H_{18}$ recently synthesized by Sondheimer and Wolovsky cannot possibly be planar as a result of steric forces. The most likely deformation is one of D_{3d} symmetry in which the six inner hydrogen atoms suffer displacements of the order of $\pm 0{\cdot}9$ Å perpendicular to the mean plane. The resulting loss of π-electron resonance energy is about 70 kcal/mole.

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IN a recent paper[1] Sondheimer and Wolovsky have reported the successful synthesis of cycloöctadecanonaene $C_{18}H_{18}$ (Fig. 1). They claimed that this hitherto unknown molecule showed definite aromatic character, being strikingly more stable than its acyclic analogue, although not so stable as a classical benzenoid system. From some preliminary considerations they suggest that the molecule should be exactly, or nearly,

FIG. 1.

planar. Shortly afterwards Davies[2] published some theoretical calculations for this molecule, using the standard molecular-orbital (M.O.) method for π-electrons in the Hückel form. He also assumed that the molecule was planar. But steric considerations (see later) show that this cannot be the case, so that a reconsideration of some of his results seems to be necessary. In this paper we propose to discuss the shape of this molecule, and shall make predictions concerning the most probable type of deformation.

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[1] F. Sondheimer and R. Wolovsky, *Tetrahedron Letters* No. 3, 3 (1959).

[2] D. W. Davies, *Tetrahedron Letters* No. 8, 4 (1959).

At first we shall suppose that, as a result of π-electron resonance, all the C—C bond lengths are equal, with a value 1·40 Å, and that all the bond angles are equal to 120°. There may be some slight failure in this assumption. Thus Ooshika[3] and Longuet-Higgins and Salem[4] have shown that in sufficiently long conjugated planar molecules the configuration with equal bond lengths is at most metastable. The stable configuration is characterized by an alternation of bond lengths, with a difference of about 0·035 Å. According to Longuet-Higgins and Salem this effect is expected from $C_{24}H_{24}$ upwards, though it cannot definitely be excluded in $C_{18}H_{18}$. However, in some unpublished calculations by one of us (A. G.) it seems likely that the higher, rather than the lower, value is the more probable.

Let us number the atoms as in Fig. 1, and let z_i and h_i denote any possible displacements of carbon atom i and hydrogen atom i' from an original assumed planar configuration where all z_i and h_i are zero. Now if the C—C bond lengths are equal to 1·40 Å and the angles are all 120°, it follows that in a hypothetical plane configuration the distance between neighbouring hydrogen atoms "inside" the molecule would be only 1·72 Å. This is exceedingly unlikely, because the shortest H . . . H distances in aliphatic hydrocarbon crystals are known to be 2·49–2·50 Å.[5] We must therefore expect some molecular deformation. There seem to be two extreme ways of maintaining the usual van der Waals distances:

(a) a change of C—C bond lengths, and perhaps a simultaneous change of bond angles, keeping the molecule planar,

(b) a buckling of some part or parts of the molecule out of the plane. We can easily show that there is very little probability for (a), because it involves too large a set of changes in bond lengths and bond angles. For example, if we remove the overcrowding by an equal increase in all C—C bond distances, these must be changed from 1·40 Å to 1·74 Å. Such an increase requires very large energy. And we know, from earlier theoretical and experimental arguments for other molecules of polynuclear type,[5] that this type of relief of steric strain is energetically far less satisfactory than out-of-plane buckling, as in (b). We have made some calculations to verify that this is also true for $C_{18}H_{18}$, and shall show later that (b) really is much more probable.

Deformations of type (b)

We make use of the method developed by Coulson and Senent[5,6], and some extensions obtained by the present authors.[7] According to this method we set up the total vibronic potential energy of the molecule $V(z_i, h_i)$, and choose the displacements z_i and h_i so that V is a minimum. So we set

$$\frac{\partial V}{\partial z_i} = 0 \qquad \text{for all } z_i \tag{1}$$

and

$$\frac{\partial V}{\partial h_i} = 0 \qquad \text{for all external hydrogens} \tag{2}$$

For the internal hydrogens we suppose (see later) that the displacements from the

[3] Y. Ooshika, *J. Phys. Soc. Japan* **12**, 1238, 1246 (1957).
[4] H. C. Longuet-Higgins and L. Salem, *Proc. Roy. Soc.* A **251**, 172 (1959).
[5] C. A. Coulson and S. Senent, *J. Chem. Soc.* 1819 (1955).
[6] C. A. Coulson and S. Senent, *J. Chem. Soc.* 1813 (1955).
[7] C. A. Coulson and A. Golebiewski, in press.

planar configuration are such that the difference between the z-values of all adjacent internal hydrogen atoms is at least equal to R, the particular value of R being such that the conventional van der Waals distances are preserved. There are actually 30 equations of types (1) and (2), but on account of the molecular symmetry this number is reduced to only 3 functionally different equations.

Following the notation of references 5–7 we let the ratio of the bond lengths r_{CC}/r_{CH} ($A_{ii'}$) be denoted by λ, so that $\lambda = 1{\cdot}40/1{\cdot}08 = 1{\cdot}2963$, and we note that $A_{i,i+1} = 1$ since all C—C bonds are supposed equal. Let us also put

$$\xi_i = \lambda h_i \tag{3}$$

and $\chi = \dfrac{k_2}{k_1}$ = ratio of torsion and out-of-plane force constants

$$= \frac{0{\cdot}0603}{0{\cdot}1345} = 0{\cdot}4483 \tag{4}$$

where the values of k_1 and k_2 are taken from our other paper.[7] In the same way as there, equations (1) and (2) now take the form:

$$\frac{1}{k_1}\frac{\partial V}{\partial z_1} = \alpha z_1 - \beta z_2 + z_3 - \chi z_4 - \chi z_{16} + z_{17} - \beta z_{18} - \gamma\xi_1 + (1-\chi\lambda)\xi_2 + \chi\xi_3 + \chi\xi_{17} + (1-\lambda\chi)\xi_{18} = 0 \tag{5}$$

$$\frac{1}{k_1}\frac{\partial V}{\partial z_2} = -\beta z_1 + \alpha z_2 - \delta z_3 + z_4 + \chi(z_5 + z_{17}) + (\gamma - \lambda - 1)z_{18} + (1-\lambda\chi)\xi_1 - \gamma\xi_2 + \varepsilon\xi_3 - \chi(\xi_4 + \xi_{18}) = 0 \tag{6}$$

$$\frac{1}{k_1}\frac{\partial V}{\partial \xi_2} = (1-\lambda\chi)z_1 - \gamma z_2 + \varepsilon z_3 + \chi(z_4 - z_{18} + \xi_1) + (1+2\chi)\xi_2 - \chi\xi_3 = 0 \tag{7}$$

where

$$\begin{aligned} \alpha &= (2+\lambda)^2 + 2 + \chi(2\lambda^2 - 4\lambda + 4) = 13{\cdot}8409 \\ \beta &= 4 + 2\lambda - \chi(\lambda^2 - 1) = 6{\cdot}2876 \\ \gamma &= 2 + \lambda + 2\chi(\lambda - 1) = 3{\cdot}5620 \\ \delta &= 4 + 2\lambda + \chi(\lambda^2 - 4\lambda + 3) = 6{\cdot}3663 \\ \varepsilon &= 1 - \chi(2 - \lambda) = 0{\cdot}6845 \\ \lambda &= 1{\cdot}2963 \\ \chi &= 0{\cdot}4483 \end{aligned} \tag{8}$$

and the remaining equations can be written down by an appropriate permutation of indices. We have not yet made any assumptions as to the symmetry of the deformed molecule. It is natural to expect that the molecule will become "corrugated" in such a way as to preserve D_{3d} symmetry. But we have also considered the alternative possibilities C_{3v}, D_3, C_s. Since, however, these all lead to greater strain energies, we shall not report any details of the calculation, and shall only describe the D_{3d} case, in which the central hydrogen atoms have displacements $\pm\frac{1}{2}R = 0{\cdot}907$ Å. Nor shall we consider any deformations of still lower symmetry. In the D_{3d} case the equations (5)–(7) take the simpler form

$$\begin{aligned} &(\alpha + 2\chi)z_1 - 2(1+\beta)z_2 + 2(1-\chi-\lambda\chi)\xi_2 \\ &\quad = \tfrac{1}{2}\gamma\lambda R - (1+\beta)z_1 + (\alpha - 2\chi + \gamma - \lambda + \delta - 1)z_2 - (\gamma + \varepsilon + \chi)\xi_2 \\ &\quad = -\tfrac{1}{2}(1+\chi-\lambda\chi)\lambda R(1-\lambda\chi-\chi)z_1 - (\gamma+\varepsilon+\chi)z_2 + (1+3\chi)\xi_2 = -\tfrac{1}{2}\chi\lambda R \end{aligned} \tag{9}$$

with solution

$$z_1 = 0{\cdot}1571\ R \quad = 0{\cdot}2850\ \text{Å}$$
$$z_2 = 0{\cdot}0009\ R \quad = 0{\cdot}0017\ \text{Å}$$
$$h_2 = -0{\cdot}0926\ R = -0{\cdot}1680\ \text{Å}$$
$$h_1 = \tfrac{1}{2}\ R \quad = 0{\cdot}907\ \text{Å (assumed).} \qquad (10)$$

The other displacements follow from symmetry. The corresponding numerical value of the strain function V is

$$V = 0{\cdot}4848\ 10^{-11}\ \text{ergs/molecule} = 69{\cdot}8\ \text{kcal/mole.} \qquad (11)$$

Deformation of type (a)

We must now examine the relative energies of strain in out-of-plane buckling (b) and in-plane deformation (a). The most fundamental procedure would be to

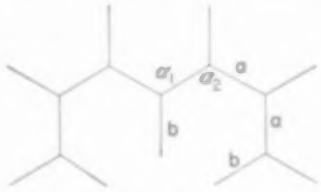


FIG. 2.

consider all possible deformations simultaneously. But this would be very tedious, and will not be necessary if we can show that the out-of-plane deformation energy V_z is much less than all reasonable in-plane deformation energies. For these latter we consider

(1) V_a, caused by appropriate change of bond angles alone, chosen in such a way that the molecule remains planar and of symmetry D_{6h}.

(2) V_c, caused by changes in C—C bond lengths alone, still preserving symmetry D_{6h}.

In case (1) it can be seen from simple trigonometric considerations (Fig. 2) that the bond angles must become:

$$\alpha_1 = 2\alpha_2 - 2\pi/3,\ \alpha_2 = \sin^{-1}\left\{\frac{R_H + b - a}{2a}\right\} \text{ where } R_H \text{ is the H . . . H distance } 2{\cdot}49\ \text{Å} \qquad (12)$$

On putting $\Delta\alpha_1 = \alpha_1 - 2\pi/3$, $\Delta\alpha_2 = \alpha_2 - 2\pi/3 = \frac{1}{2}\Delta\alpha_1$ and using the potential function developed by Crawford and Miller[8] for the in-plane vibrations of benzene (but with neglect of the small terms representing *meta*- and *para*-interaction constants) we find that

$$V_a = 5{\cdot}9 \times 10^{-11}\ \text{erg/molecule}$$

This is about twelve times as large as the out-of-plane V_z given by (11).

Similarly in case (2) we remove the H . . . H overcrowding by increasing each

[8] B. L. Crawford and F. A. Miller, *J. Chem. Phys.* **17**, 249 (1949).

C—C bond by 0·34 Å. The total energy which is thereby needed (once again neglecting *meta*- and *para*-interactions) is

$$V_c = 8{\cdot}1 \times 10^{-11} \text{ erg/molecule},$$

which is about seventeen times as large as V_z.

Because V_α and V_c have comparable values, we could reduce the strain energy by simultaneous change in both bond lengths and bond angles; and the deformation energy would be not smaller than

$$\tfrac{1}{2}(V_\alpha + V_c) \sim 7 \times V_z$$

These calculations justify our conclusion that in the real molecule the release of steric overcrowding will take place almost entirely by out-of-plane displacements, and our

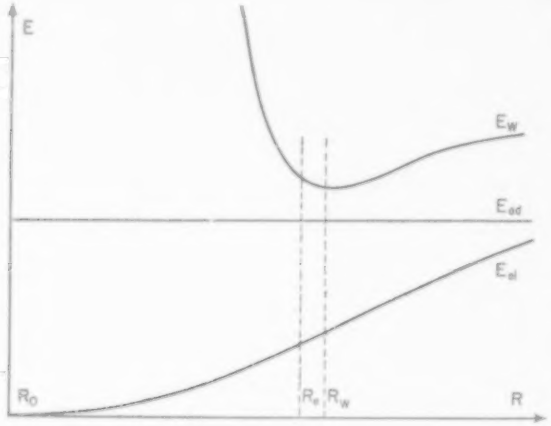


FIG. 3.

value of 69·8 kcal/mole will be a good approximation to the best value that could be obtained by simultaneous adjustment of all the molecular parameters.

General conclusions

It is interesting to use the results just obtained to plot total energy curves for this molecule. But instead of adopting the final value of R involved in the hydrogen displacements, let us use R as a parameter, and plot (Fig. 3) the variation with R of:

(I) $E_{el}(R)$, defined as the total electronic energy of the system. This is the quantity which we have effectively been calculating hitherto, and takes account of the loss of π-electron energy due to the displacements z_i and h_i, but it does not include the H . . . H van der Waals energy,

(II) E_w, defined as the total van der Waals energy of the six central hydrogen atoms. This is approximately equal to six times the van der Waals energy between a pair of H atoms.

(III) E_{ad}, defined as the sum of the tabulated energies of the single and double bonds that occur in a Kekulé structure. Thus, in the absence of E_w, the conventional resonance energy would be simply $E_{ad} - E_{el}$. In Fig. 3 we have also used R_w to denote that value of R which leads to the usual van der Waals distance 2·49 Å.

But of course the true equilibrium value of R, here called R_e, will be a little less than R_w, since R_w is at the minimum of the E_w curve, and R_e is at the minimum of the $(E_{el} + E_w)$ curve. The length $R_w - R_e$ will be small, since we know that the repulsive part of the E_w curve rises very steeply.

If we define the resonance energy E_{res} as the difference between the energy of a Kekulé structure (E_{ad}), without any van der Waals correction, and the equilibrium total energy, then

$$E_{res} = E_{ad} - \{E_{el}(R_e) + E_w(R_e)\} \tag{13}$$

This is not the same as the value calculated by Davies[2] who neglected E_w and calculated E_{el} only for the planar molecule; in fact

$$E_{Davies} = E_{ad} - E_{el}(0) = 103 \text{ kcal/mole} \tag{14}$$

Our own calculations (11) of V are

$$V = E_{el}(R_w) - E_{el}(0) \tag{15}$$

It follows that

$$\begin{aligned} E_{Davies} - E_{res} &= \{E_{el}(R_e) - E_{el}(0)\} + E_w(R_e) \\ &= \{E_{el}(R_e) - E_{el}(R_w)\} + V + E_w(R_e) \end{aligned}$$

Now the total energy at R_e will be very slightly less than at R_w. So

$$E_{el}(R_e) + E_w(R_e) < E_{el}(R_w) + E_w(R_w),$$

from which it follows that

$$E_{Davies} - E_{res} < V + E_w(R_w) \tag{16}$$

So $E_{res} > E_{Davies} - V - E_w(R_w)$. Substituting for E_{Davies} and V we see that E_{res} should be a little more than $33 - E_w(R_w)$ kcal/mole. Thus the resonance energy is much smaller than its value for a benzenoid system with no overcrowding, and of the same order of magnitude as for an acyclic analogue. The molecule would, however, be expected to show aromatic-type behaviour in its reactivity, in general agreement with Sondheimer and Wolovsky.

There is, however, one difficulty connected with the spectrum of $C_{18}H_{18}$ in the u.v. range. Davies[2] calculated an N → V transition at 6030 Å, using the standard Hückel technique. But the experimental value is 4080 Å. This big difference would be still further increased if steric effects on the spectra were to be introduced in a way such as that discussed by one of us.[9] For these steric effects lead to red shifts and so increase the calculated wavelength. Perhaps, therefore, the model which is being used is not correct. If, for example, the bonds alternated in length along the carbon chain, then by analogy with the linear polyene chains we should expect a considerable blue shift relative to the value calculated by Davies. The X-ray work announced by Sondheimer and Wolovsky[1] will probably settle this question. But even if the bonds do alternate in this way, this is very unlikely to affect our discussion of the strain energy and the magnitudes of the various atomic displacements other than in a relatively minor way.

Acknowledgements—One of us (A. G.) would like to acknowledge the award of a Fellowship from The Rockefeller Foundation which has made this work possible.

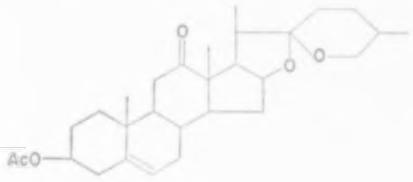
[9] C. A. Coulson, *Steric Effects in Conjugated Systems* [Proceedings of a Symposium by The Chemical Society, The University, Hull, 15–17 July (1958)] pp. 8–21. Butterworths, London (1958).

Tetrahedron, 1960, Vol. 11, p. 131. Pergamon Press Ltd. Printed in Northern Ireland

ERRATUM

M. E. WALL and S. SEROTA: Steroidal sapogenins—LXII. 12-Methyl hemiketals derived from 12-keto-16-dehydropregnenes, *Tetrahedron* **10,** 238 (1960).

Formula II on p. 239 of the above article should read:



II

Tetrahedron, 1960, Vol. 11, p. 132. Pergamon Press Ltd. Printed in Northern Ireland

A list of papers to be published in the next issue

B. S. Joshi, R. Srinivasan, R. V. Talavdekar and K. Venkataraman: Derivatives of 1,3,5-triazine—I. Condensation of *o*-hydroxybenzanilides with cyanuric chloride and fission of the triazine ring.

P. Madhavan Nair, R. Srinivasan and K. Venkataraman: Condensation of 2,4-dinitrochlorobenzene with *o*-hydroxyarylamides.

A. M. Roe and M. Gates: A degradation of gelsemine.

E. D. Bergmann and S. Yaroslavsky: Experiments in the 4-arylcycloalk-2-en-1-one series—IV. 4-Phenylcyclohepta-1,3-dione.

S. Yaroslavsky and E. D. Bergmann: Substituted 6,7-benzocoumaran-2-ones from the Stobbe reaction of benzyl ketones.

N. L. Wendler, D. Taub and R. W. Walker: Equilibrium relationship of D-homo ketolic systems.

M. C. Caserio, W. H. Graham and J. D. Roberts: Small-ring compounds—XXIX. A reinvestigation of the solvolysis of cyclopropylcarbinyl chloride in aqueous ethanol isomerization of cyclopropylcarbinol.

W. von E. Doering and D. W. Wiley: Heptafulvene (methylenecycloheptatriene).

B. Fuchs and H. J. E. Loewenthal: The contraction of ring A in 5α-cholestane derivatives.

Tetrahedron, 1960, Vol. 11, pp. 133 to 139. Pergamon Press Ltd. Printed in Northern Ireland

DERIVATIVES OF 1,3,5-TRIAZINE—I*

CONDENSATION OF *o*-HYDROXYBENZANILIDES WITH CYANURIC CHLORIDE AND FISSION OF THE TRIAZINE RING

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National Chemical Laboratory, Poona

VOL. 11 1960

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Abstract—The condensation of cyanuric chloride with *o*-hydroxybenzanilides takes place on the amide nitrogen. Treatment of the condensation products with acetic anhydride and pyridine opens the triazine ring and yields benzoxazine derivatives, whose structures are discussed.

DYES containing the 1,3,5-triazine nucleus, prepared by suitable condensations with cyanuric chloride, have been the subject of numerous patents.[1,2] Fierz-David and Matter[3] were the first to study the preparation of dyes of this type, and there is no reference in the literature to any later investigation of the constitution of cyanurated dyes. The main function of the triazine ring was to act as a chromophoric insulator, enabling the combination of azo or other dye units to form more complex dyes, and for this purpose cyanuric chloride had several advantages over phosgene. Very recently chromogens attached to cyanuric chloride, leaving one or two chlorine atoms free for direct chemical combination with cellulose, have been marketed as "reactive dyes" (Procions, I.C.I., Cibacrons, Ciba), constituting a landmark in the history of synthetic dyes.

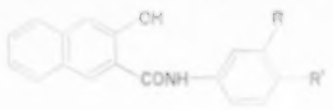
Some years ago one of us prepared azoic coupling components by condensing 1, 2 or 3 molecules of the *m*- or *p*-aminoanilide (I; R or $R^1 = NH_2$; R^1 or R = H) of 2-hydroxy-3-naphthoic acid with one molecule of cyanuric chloride, but the shades produced on cotton by coupling with diazonium salts were of no practical interest, although some of the "naphthols" (e.g. II) had excellent affinity for the fibre.[4]

In connection with this work it was subsequently observed that 2-hydroxy-3-naphthanilide (Naphtol AS) itself condensed with cyanuric chloride in presence of ethanolic sodium hydroxide. The reaction takes place on the NH and not the OH group, and the product, colourless needles, m.p. 182°, has the structure III, as shown by its alkali solubility and ability to couple with diazonium salts. It can be dissolved in 1 per cent sodium hydroxide solution at 0° and recovered unchanged after a few minutes by acidification. Salicylanilide similarly yielded IV. Although the products III and IV are soluble in aqueous sodium hydroxide, they do not give a ferric coloration, unlike 2-hydroxy-3-naphthanilide and salicylanilide. The infra-red spectra of III and IV show a hydroxyl band around 3350 cm^{-1}, a carbonyl band around 1670 cm^{-1}, and strong absorption bands in the 1505, 1260 and 850 cm^{-1} regions which

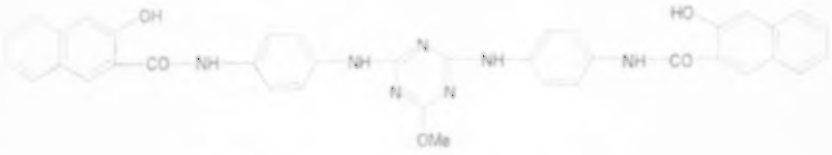
* Communication No. 410 from the National Chemical Laboratory Poona, India.

[1] K. Venkataraman, *The Chemistry of Synthetic Dyes* Vol. I, p. 583; Vol. II, pp. 864, 891. Academic Press, New York (1952).
[2] E. M. Smolin, and L. Rapoport, *s-Triazines and Derivatives*. Interscience, New York (1959).
[3] H. Fierz-David and M. Matter, *J. Soc. Dyers Colourists* 53, 424 (1937).
[4] R. V. Talavdekar, Ph.D. Thesis, Univ. of Bombay (1951).

are characteristic of cyanuric chloride.[2] 2-Hydroxy-3-naphthanilide and salicylanilide show no hydroxyl band; in the carbonyl region an absorption band at 1612 cm^{-1} indicates strong chelation. Benzanilide did not react with cyanuric chloride; and in *p*-hydroxybenzanilide (conveniently prepared by refluxing *p*-hydroxybenzoic acid in toluene with phenyl phosphazoanilide)[3] the phenolic hydroxyl reacted to form the

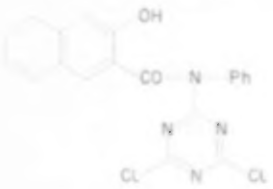


I

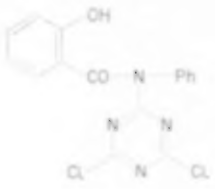


II

alkali-insoluble product V. The azoic alkali-insoluble pigment obtained by coupling 2-hydroxy-3-naphthanilide with diazotized aniline failed to react with cyanuric chloride, showing the need for a hydroxyl group capable of ready interaction with a base, the mechanism of which is discussed in the following paper.



III



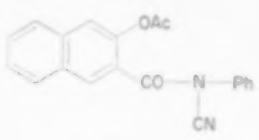
IV

V

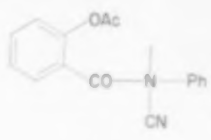
Boiling acetic anhydride left III and IV unaffected, but in presence of a few drops of pyridine they led to crystalline compounds which were free from chlorine and were obviously not the simple O-acetyl derivatives. Two products were obtained in each case: one on cooling the acetic anhydride solution and the other on dilution of the mother-liquor. The products A, m.p. 288°, and B, m.p. 304°, from III analysed respectively for $C_{20}H_{14}N_2O_3$ and $C_{15}H_{11}NO_2$. Similarly IV gave compounds C, m.p. 243°, and D, m.p. 242°, analysing respectively for $C_{16}H_{12}N_2O_3$ and $C_{14}H_9NO_3$. The formulae of A and C corresponded to structures VI and VII, but the infra-red

[3] H. W. Grimmel, A. Guenther and J. F. Morgan, *J. Amer. Chem. Soc.* **68**, 539 (1946).

spectra did not show the characteristic —C≡N stretching vibration in the 2220 cm^{-1} region. The condensation of acetylsalicyl chloride with phenylcyanamide in pyridine solution gave a product with the authentic structure VII, m.p. 141°; the infra-red spectrum had a band at 2230 cm^{-1} corresponding to the —C≡N stretching vibration. Compound C therefore did not have the structure VII.

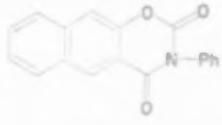


VI

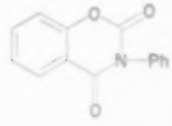


VII

When compound A was heated with 10 per cent sodium hydroxide solution, 2-hydroxy-3-naphthanilide was recovered, and A was converted to B by heating with 10 per cent hydrochloric acid or dissolving in conc sulphuric acid and pouring into water. Compound C behaved similarly, yielding salicylanilide by alkaline hydrolysis and compound D by treatment with sulphuric acid. Both B and D were insoluble in sodium hydroxide solution. The infra-red spectrum of B showed bands at 1764 cm^{-1} (lactone) and 1686 cm^{-1} (carbonyl absorption of tertiary amide). Compound D exhibited similar absorption bands at 1756 cm^{-1} and 1680 cm^{-1}. Neither B nor D showed a band due to a phenolic hydroxyl group in the 3350 cm^{-1} region. Structures VIII and IX were therefore assigned to B and D, and confirmed by an alternative synthesis using a known procedure.[6] 3,4-Dihydro-1,3,2-benzoxazine-2,4-dione (IX; phenyl replaced by hydrogen) was prepared by Einhorn and Mettler[6] by the condensation of salicylamide with ethyl chloroformate; IX was prepared earlier by Bogisch[7] by the same method, which we have now used for the synthesis of VIII. A homologue of IX has been described by Deck and Dains[8], who obtained it by heating phenyl salicylate with S-methyl-N,N-di-*o*-tolylisothiourea, followed by acid hydrolysis.



VIII

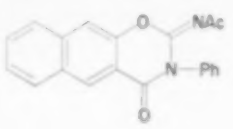


IX

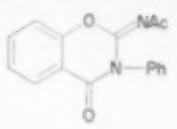
From the molecular formulae and the ease of hydrolysis to VIII and IX it was then deduced that A and C were constituted as X and XI. The infra-red spectrum of A showed bands at 1721 and 1241 cm^{-1} (acetate), 1691 cm^{-1} (carbonyl of tertiary amide), 1656 cm^{-1} (broad band indicating C=N—); C showed similar infra-red bands at 1722 and 1220, 1708, 1657 cm^{-1}. The ultra-violet absorption spectra (in ethanol) of C showed maxima at 238 mμ (log ε 4·15) and 293 mμ (log ε 3·6); and D at 238 mμ (log ε 4·21) and 288 mμ (log ε 3·54).

The formation of compounds X and XI during the acetylation of III and IV

[6] A. Einhorn and C. Mettler, *Ber. Dtsch. Chem. Ges.* **35**, 3647 (1902).
[7] Bogisch, Dissertation, Rostock (1889). Cited in *Beilstein* **27**, 263.
[8] J. F. Deck and F. B. Dains, *J. Amer. Chem. Soc.* **55**, 4986 (1933).



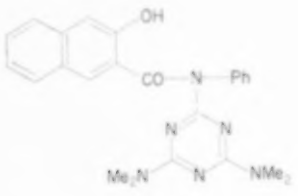
X



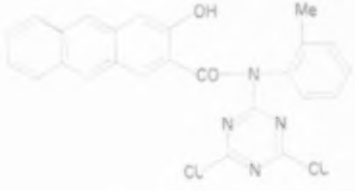
XI

provides an unusual example of the fission of the 1,3,5-triazine ring system,* apart from the parent compound which is very sensitive to hydrolysis.

The two chlorine atoms in III were readily replaceable by dimethylamino groups, yielding XII which may be of some interest as an intermediate for basic dyes. Treatment of III with 1 per cent alcoholic sodium hydroxide at 50–55° for 3 hours resulted in smooth hydrolysis to 2-hydroxy-3-naphthoic acid in 87 per cent yield, accompanied by a small amount of III in which chlorine was replaced by hydroxyl. Alkaline hydrolysis of the N-acetyl[9] and N-benzoyl derivatives led to the parent Naphtol AS (I; R and R^1 = H), together with acetic or benzoic acid. The difference in the

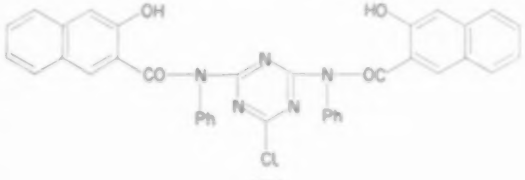


XII



XIII

hydrolytic behaviour of the N-cyanuryl derivative on the one hand and the N-acetyl and N-benzoyl derivatives on the other is to be anticipated in view of the difference between cyanuric acid and carboxylic acids; in III therefore the carbonyl group is

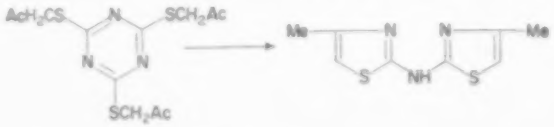


XIV

more readily attacked by hydroxyl ion than the triazine carbon attached to the amide nitrogen.

The *o*-toluidide (Naphtol AS-GR; C.I. 37585) of 2-hydroxyanthracene-3-carboxylic acid condensed with cyanuric chloride, yielding XIII. Mild alkaline

* One example in the literature is the degradation and rearrangement of 2,4,6-tri(acetonylthio)-s-triazine by the action of conc hydrochloric acid [A. Hantzsch, *Ber. Dtsch. Chem. Ges.* **61B**, 1776 (1928)].



[9] E. B. Higgins, *J. Soc. Dyers Colourists* **43**, 213 (1927).

hydrolysis of XIII gave in about 70 per cent yield 2-hydroxyanthracene-3-carboxylic acid, which is difficult to isolate when the arylamide is submitted to the usual drastic methods of hydrolysis with strong sodium hydroxide solution or conc sulphuric acid.[1]

The condensation of 2 moles of 2-hydroxy-3-naphthanilide with one of cyanuric chloride yielded XIV. Towards acetic anhydride and pyridine XIV behaved like the primary condensation product III and gave X.

EXPERIMENTAL

Condensation product (III) *of 2-hydroxy-3-naphthanilide with cyanuric chloride*

To a solution of cyanuric chloride (0·76 g) in acetone (10 ml) at 0–5° a solution of 2-hydroxy-3-naphthanilide (1·1 g) in acetone (20 ml) and 10% NaOH (1·7 ml) was added with stirring. After 1 hr ice-cold water (30 ml) was added and the mixture stirred for 15 min. The precipitate was filtered, washed, and dried *in vacuo* at room temp. It crystallized from benzene (Norit) in colourless needles, m.p. 182° (1·3 g). (Found: C, 58·6; H, 2·7; N, 14·0; Cl, 17·7. $C_{20}H_{12}Cl_2N_4O_2$ requires: C, 58·5; H, 2·9; N, 13·7; Cl, 17·3%).

Under similar conditions benzamide and benzanilide were recovered unchanged.

Hydrolysis of III

A solution of (III; 1 g) in 1% NaOH (100 ml containing 15 ml ethanol) was heated at 50–55° for 3 hr. The solution was filtered and saturated with carbon dioxide. The precipitate (0·2 g) crystallized from alcohol in colourless plates, m.p. 208–210°. (Found: N, 15·7. $C_{20}H_{14}N_4O_4$ requires: N, 15·0%). The filtrate was acidified and the precipitate (0·4 g) crystallized from dilute ethanol in yellow plates, m.p. 219–221°, alone or mixed with 2-hydroxy-3-naphthoic acid.

Condensation product (IV) *of salicylanilide with cyanuric chloride*

To a solution of cyanuric chloride (1 g) in acetone (5 ml) a solution of salicylanilide (1·1 g) in acetone (5 ml) and 10% NaOH (2·2 ml) was added and stirred at 0–5° for 1 hr. On the addition of ice-water a semi-solid mass separated and stuck to the sides of the flask. The aqueous solution was decanted off, and the residue dissolved in benzene (100 ml). The solution was dried over anhydrous calcium chloride, filtered and concentrated, and hexane added till a slight turbidity developed. On cooling, the crystalline product (0·8 g) was recrystallized from benzene–hexane. The colourless needles had m.p. 152°. (Found: C, 53·5; H, 2·9; Cl, 19·0; N, 15·0. $C_{16}H_{10}Cl_2N_4O_2$ requires: C, 53·2; H, 2·8; Cl, 19·7; N, 15·5%).

Condensation product (V) *from* p-*hydroxybenzanilide and cyanuric chloride*

The anilide (0·62 g) and cyanuric chloride (0·55 g) were dissolved in acetone (20 ml) and treated with 10% NaOH (1·2 ml) at 0–5° for 2 hr. Worked up as above the product (0·96 g) crystallized from acetone in broken plates, m.p. 228°. (Found: C, 53·5; H, 2·8; N, 15·7. $C_{16}H_{10}Cl_2N_4O_2$ requires: C, 53·2; H, 2·8; N, 15·5%).

2-*Acetimino*-3-*phenyl*-4-*keto*-3,4-*dihydro*-1,3,2-*β*-*naphthoxazine* (X)

A mixture of (III; 6 g) acetic anhydride (60 ml) and a few drops of pyridine was refluxed for 3 hr and cooled. The brown crystalline product (A) was filtered, washed and dried (2·3 g). Dilution of the filtrate with water and cooling in a refrigerator gave B (0·2 g). Crystallization of A from toluene gave colourless needles, m.p. 288°. (Found: C, 72·8; H, 4·3; N, 8·6. $C_{20}H_{14}N_2O_2$ requires: C, 72·7; H, 4·2; N, 8·5%). Crystallization of B from toluene gave colourless needles, m.p. 304° after shrinking at 268°. (Found: C, 74·4; H, 3·6; N, 4·6. $C_{18}H_{11}NO_2$ requires: C, 74·7; H, 3·8; N, 4·8%).

2-*Acetimino*-3-*phenyl*-4-*keto*-3,4-*dihydro*-1,3,2-*benzoxazine* (XI)

On refluxing (IV; 2 g) for 2 hr with acetic anhydride (20 ml) and pyridine (0·1 ml) and cooling, the product (C) was collected (0·75 g). Dilution of the filtrate with water yielded D (0·09 g). Crystallization of C from toluene gave colourless needles, m.p. 243°. (Found: C, 69·1; H, 4·3; N, 10·3.

$C_{16}H_{12}N_2O_3$ requires: C, 68·6; H, 4·3; N, 10·0%). Crystallization of D from ethanol gave colourless needles, m.p. 242°. (Found: C, 70·4; H, 4·1; N, 6·2. $C_{14}H_9NO_3$ requires: C, 70·3; H, 3·8; N, 5·9%).

O-*Acetyl*-N-*cyanosalicylanilide* (VII)

A solution of acetylsalicyl chloride (0·5 g) and phenylcyanamide (0·5 g) in pyridine (5 ml) was shaken for 1 hr at 25°. Dilution with water (100 ml) and acidification with HCl gave a product (0·25 g), which crystallized from benzene–hexane in colourless cubes, m.p. 141°. (Found: C, 69·1; H, 4·0; N, 10·0. $C_{16}H_{12}N_2O_3$ requires: C, 68·6; H, 4·3; N, 10·0%).

Alkaline hydrolysis of X

A mixture of X (0·2 g), ethanol (5 ml) and 10% NaOH (20 ml) was heated on a water-bath for 2 hr and filtered. A small amount of undissolved material (0·02 g) was identified as unchanged X. Acidification of the filtrate and crystallization of the precipitate from ethanol gave 2-hydroxy-3-naphthanilide, m.p. 245°.

Acid hydrolysis of X

(a) A solution of X (0·2 g) in conc sulphuric acid (4 ml) was kept at 25° for 30 min and then poured on ice. The precipitate crystallized from toluene in colourless needles (0·17 g), m.p. 304° (after shrinking at 265°). This was identical in its m.p. and infra-red spectrum with the by-product (VIII) obtained in the acetylation of III.

(b) On heating X (0·1 g) at 98° for 1 hr with 10% HCl (20 ml) and ethanol (5 ml), the product (0·07 g) crystallized from benzene in colourless needles, m.p. 304° (after shrinking at 265°).

Acid hydrolysis of XI

Treatment of XI (0·4 g) with conc sulphuric acid (10 ml) and dilution as above gave IX, crystallizing from ethanol in colourless needles (0·2 g), m.p. 242°, identical with IX.

3-*Phenyl*-3,4-*dihydro*-1,3,2-*benzoxazine*-2,4-*dione* (IX)

A solution of salicylanilide (2·4 g) in pyridine (15 ml) and ethyl chloroformate (1 ml) was stirred at 85° for 2 hr. The pale brown precipitate (1·01 g) obtained by pouring into ice-water crystallized from ethanol in colourless needles, m.p. 242° (Bogisch,[7] m.p. 246° corr).

3-*Phenyl*-3,4-*dihydro*-1,3,2-*β-naphthoxazine*-2,4-*dione* (VIII)

2-Hydroxy-3-naphthanilide (1·4 g) was suspended in pyridine (25 ml) and heated with ethyl chloroformate (1 ml) for 3 hr at 80–85° with agitation. The precipitate obtained by pouring on ice was collected, shaken with ethanol (20 ml), 10% NaOH (5 ml) and diluted with water (50 ml). This gave a precipitate (0·56 g), which crystallized from toluene in colourless needles, m.p. 304° after shrinking at 265°. From the alcoholic alkaline filtrate unchanged 2-hydroxy-3-naphthanilide (0·8 g) was recovered.

N-*Benzoyl*-2-*hydroxy*-3-*naphthanilide*

Benzoylation of 2-hydroxy-3-naphthanilide was effected in alcoholic NaOH by benzoyl chloride at 0–5°, molar proportions being used and the mixture stirred until it was neutral to Brilliant Yellow. The product crystallized from benzene (in which 2-hydroxy-3-naphthanilide is insoluble) in colourless needles, m.p. 189–190°. (Found: N, 4·2. $C_{23}H_{17}O_3N$ requires: N, 3·8%).

Hydrolysis of N-*benzoyl*-2-*hydroxy*-3-*naphthanilide*

The compound (0·5 g) was heated with 10% NaOH (5 ml), water (40 ml) and alcohol (5 ml) for 3 hr at 50°. The solution was saturated with CO_2 and the precipitate (0·35 g) was identified as 2-hydroxy-3-naphthanilide.

Primary condensation product (XIII) *from the* o-*toluidide of* 2-*hydroxyanthracene*-3-*carboxylic acid and cyanuric chloride*

Prepared as in the case of III, the product crystallized from benzene in pale yellow needles, m.p. 210°. (Found: Cl, 14·7; N, 11·6. $C_{25}H_{16}O_2Cl_2N_4$ requires: Cl, 15·0; N, 11·8%).

Treatment of XIII (1·5 g) in alcohol (50 ml) and water (100 ml) with 10% NaOH (15 ml) at 50–55° for 3 hr, cooling, and saturating with CO_2 gave a minute amount of a precipitate which was rejected. Acidification of the filtrate gave a yellow precipitate, which crystallized from glacial acetic acid in orange-yellow plates (0·55 g), m.p. 293–294° (dec). (Found: C, 75·1; H, 3·9. Calc. for $C_{13}H_{10}O_3$: C, 75·6; H, 4·2%).

2,4-*Bis-dimethylamino*-6-N-2′-*hydroxy*-3′-*naphthoylanilino*-1,3,5-*triazine* (XII)

To a stirred solution of III (0·5 g) in dimethylformamide (50 ml) 30% aqueous dimethylamine (0·4 ml) and sodium carbonate (0·08 g) in water (10 ml) were added. After heating on a water-bath for 3 hr, the solution was poured into water (150 ml) and extracted with ether. Ether was removed and the residue crystallized from ethanol in colourless needles (0·21 g), m.p. 183°. (Found: C, 67·5; H, 5·8; N, 19·5. $C_{24}H_{24}O_2N_6$ requires: C, 67·3; H, 5·6; N, 19·6%).

Secondary condensation product (XIV) *from* 2-*hydroxy*-3-*naphthanilide and cyanuric chloride*

To a stirred solution of cyanuric chloride (0·38 g) in acetone (10 ml) at 0–5°, a solution of 2-hydroxy-3-naphthanilide (1·1 g) in ethanol (20 ml) and 10% NaOH (1·7 ml) was added. The solution was stirred at 0–5° for 1 hr and then at 45–50° for 1 hr. Water (40 ml) was added and the precipitate (1·22 g) crystallized from chlorobenzene. The colourless plates had m.p. 206°. (Found: C, 69·8; H, 4·1; Cl, 5·8; N, 10·6. $C_{27}H_{24}O_4ClN_5$ requires: C, 69·6; H, 3·8; Cl, 5·6; N, 11·0%). This compound on treatment with acetic anhydride and pyridine under the conditions described in the case of III yielded X.

Acknowledgements—We are indebted to the Council of Scientific and Industrial Research for a Junior Fellowship (to R. Srinivasan), to Imperial Chemical Industries, Limited (Dyestuffs Division) for a grant (to R. V. Talavdekar), to Dr. T. S. Gore and Mr. V. S. Pansare for the microanalyses, and to Mr. C. I. Jose for the infra-red spectra.

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CONDENSATION OF 2,4-DINITROCHLOROBENZENE WITH *o*-HYDROXYARYLAMIDES*

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National Chemical Laboratory, Poona

(*Received* 9 *June* 1960)

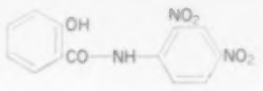
Abstract—*o*-Hydroxyarylamides react readily with 2,4-dinitrochlorobenzene in presence of bases to give the N-2,4-dinitrophenyl derivatives. The reaction appears to proceed by a direct displacement of the halogen by the amide nitrogen involving intramolecular nucleophilic catalysis by the phenoxide oxygen; but a Smiles rearrangement is not completely excluded. The N-dinitrophenyl derivatives are stable to boiling hydrochloric acid, but are hydrolysed easily by aqueous sodium carbonate or hydroxide. Condensation with dinitrochlorobenzene, followed by mild alkaline hydrolysis, is a useful procedure for determining the constitution of azoic coupling components of the Naphtol AS type. Thus Naphtol AS–RS and AS–KN have been shown to be the 4-chloro-2-methoxy-5-methylanilide of 2-hydroxy-3-naphthoic acid and the α-naphthylamide of 3-hydroxydibenzofuran-2-carboxylic acid respectively.

THE Sanger method for determining the amino acid sequence in a protein depends on the condensation of 2,4-dinitrofluorobenzene (DNFB) with free amino groups at room temperature in sodium bicarbonate solution, leaving amide groups unaffected, and on the subsequent hydrolysis of the terminal amide group by hydrochloric acid.[1] Since *o*-hydroxybenzanilides condense with cyanuric chloride, the amide nitrogen and not the phenolic oxygen being attacked,[2] it appeared probable that they would react similarly with DNFB. The amide groups in salicylamide, salicylanilide and 2-hydroxy-3-naphthanilide have now been found to react readily with DNFB in presence of ethanolic sodium hydroxide at about 50° or triethylamine in dimethylformamide (DMF)[3] at room temperature. The amide group in benzamide and benzanilide are unreactive towards DNFB as well as cyanuric chloride; and likewise the hydroxyl group in *p*-hydroxybenzanilide is attacked by both the reagents. In the Sanger procedure DNFB is preferred to the much commoner DNCB, because the latter requires heat for the condensation, resulting in a certain amount of hydrolysis of the protein.[1,4] DNCB, however, is adequate for the reaction with *o*-hydroxybenzamides; the products (I, II, III) are in fact more easily crystallizable than those obtained when DNFB is used.

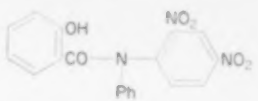
The inability of an amide group to react with DNCB is the result of the amide resonance (IVA ↔ IVB) and the consequent lowering of the basicity or nucleophilic reactivity of the nitrogen atom. In the amide or anilide of salicylic acid the amide resonance is weakened considerably by the participation of the CO group in a chelate ring, stabilized by resonance between structures VA and VB.

* Communication No. 409 from the National Chemical Laboratory, Poona, India.

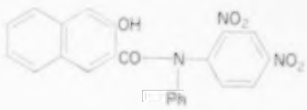
[1] F. Sanger, *Biochem. J.* **39**, 507 (1945).
[2] B. S. Joshi, R. Srinivasan, R. V. Talavdekar and K. Venkataraman, preceding paper.
[3] M. L. Wolfrom, B. O. Julian, M. S. Toy and A. Chaney, *J. Amer. Chem. Soc.* **81**, 1446 (1959).
[4] E. Abderhalden and W. Stix, *Hoppe-Seyler's Z.* **129**, 143 (1923).



I



II



III

IV A IV B

V A V B

The basicity of the nitrogen atom is therefore greater than in benzamide, and a nucleophilic attack on DNCB becomes possible. In the absence of sodium hydroxide, when the above mechanism may be pictured, the reaction proceeds very slowly; the yield of the dinitrophenyl derivative (III) is only about 5 per cent in boiling nitrobenzene after 4 hours.

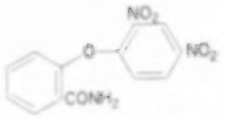
Another conceivable explanation for the reactivity of the amide nitrogen is that hydrogen bonding of an amide hydrogen with the phenolic oxygen in the transition state for the displacement may lower the activation energy for the reaction. An *o*-methoxyl group should then be more effective than an *o*-hydroxyl in increasing the reactivity. It was found however that the anilide of *o*-methoxybenzoic acid did not react with DNCB.

The reactivities observed when this reaction takes place in the presence of a base are very much greater, indicating the operation of a different mechanism. The reaction may proceed either by a direct attack of DNCB on the amide nitrogen or through the prior formation of the diphenyl ether and subsequent migration of the dinitrophenyl group to the amide nitrogen atom. In alkaline solution *o*-hydroxybenzamides and *o*-hydroxybenzanilides will exist in the conformation indicated in VIA and VIB, wherein the oxygen atoms carrying partial negative charges are farthest apart and there is hydrogen bonding between the phenolic oxygen and the amide hydrogen atoms.

VI A VI B

The affinity of the anion of 2-hydroxy-3-naphthanilide for cellulose has been explained on the basis of similar structures[5]. The nucleophilic reactivity of the amide nitrogen in these cases may be expected to be of the same order as that of amines, and a reasonable mechanism for the reaction is the direct displacement of the halogen from DNCB by the amide nitrogen. The interaction between the phenoxide oxygen and the amide hydrogen will be stronger in the transition state for the reaction than in the species (VI) itself. Intramolecular nucleophilic catalysis of this type has been observed by Zimmering *et al.*[6] in a study of the rate of imidization of a copolymer of methacrylic acid with maleic anhydride, which was treated with *p*-nitroaniline. The anilide groups are surrounded by *β*-carboxylic acid groups on either side in the polymer chain. The velocity of imidization goes through a maximum at pH 5 and corresponds to the following mechanism for the reaction.[6,7]

A hydrogen bridge of this type cannot occur in the transition state for the reaction of *p*-hydroxybenzanilide with DNCB. The amide nitrogen atom therefore remains inactive and the phenoxide end of the molecule makes the normal nucleophilic attack on DNCB leading to the formation of the dinitrophenyl ether.



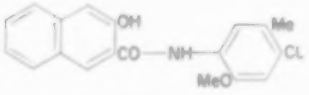
VII

The alternative path for the reaction may now be briefly considered and compared with the mechanism already discussed. Tozer and Smiles[8] prepared the 2,4-dinitrophenyl ether (VII) of salicylamide by condensing methyl salicylate with DNCB in presence of sodium methoxide in methanol, and converting the ester to the amide via the acid and acid chloride; they found that VII rearranged to salicyl-2,4-dinitroanilide (I) by treating with a solution of sodium hydroxide in aqueous acetone at 18° for 2 minutes or by heating it at 200°. They also synthesized I by shaking DNCB with an ethanolic solution of salicylamide and sodium ethoxide. A mechanism involving a Smiles rearrangement looks entirely plausible for the reaction under discussion. In an attempt to choose between these two mechanisms we have determined the relative reactivities of salicylanilide, *p*-hydroxybenzanilide, N-methylsalicylanilide and aniline towards DNCB in dimethylformamide in presence of triethylamine. It has been found that N-methylsalicylanilide and *p*-hydroxybenzanilide react to the extent

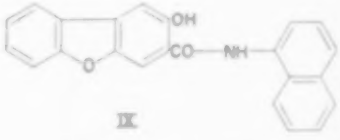
[5] K. Venkataraman, *The Chemistry of Synthetic Dyes* Vol. I, p. 681. Academic Press, New York (1952).
[6] E. W. Westhead, Jr. and H. Morawetz, *J. Amer. Chem. Soc.* **80,** 237 (1958); P. E. Zimmering, E.W. Westhead, Jr. and H. Morawetz, *Biochim. Biophys. Acta* **25,** 376 (1957).
[7] M. L. Bender, *Chem. Rev.* **60,** 87 (1960).
[8] B. T. Tozer and S. Smiles, *J. Chem. Soc.* 2052 (1938).

of 13 per cent and 34 per cent respectively in one hour at about 66°. Under the same conditions aniline undergoes 45 per cent reaction. The normal phenoxide reactivity towards DNCB which is greater than that of aniline is found to be depressed strongly by the presence of carbonyl groups in the *ortho* and *para* positions. This lowering of reactivity is greater in the *o*-isomer because of the additional steric factor involved. If the second mechanism involving a Smiles rearrangement is operating in the reaction, it may be expected that the reactivity of salicylanilide will be less than that of *p*-hydroxybenzanilide and close to that of N-methylsalicylanilide.* Actually we find that salicylanilide gives under comparable conditions about 53 per cent of the N-dinitrophenyl derivative, which exceeds by more than 50 per cent the reactivity of *p*-hydroxybenzanilide and is even greater than that of aniline. This is the kind of behaviour to be expected from the first mechanism involving intramolecular nucleophilic catalysis. It should be mentioned that there are side reactions accompanying the formation of the N-dinitrophenyl derivative from salicylanilide. The amount of DNCB used up in the reaction, when an equimolecular proportion of the reagents was employed, was measured by estimating the chloride liberated and corresponds to 88 per cent reaction.

Like the cyanuric chloride derivatives the N-dinitrophenyl derivatives are readily hydrolysed by alkali, but they are very stable to acid. By heating with 1 per cent aqueous sodium hydroxide at 75–80° for 3 hours or refluxing with 10 per cent aqueous sodium carbonate for 14 hours the hydrolysis of III to 2-hydroxy-3-naphthoic acid and 2,4-dinitrodiphenylamine is complete. One advantage of the dinitrophenyl derivatives from the point of view of using them for determining the constitution of azoic coupling components of the Naphtol AS type is that the aromatic amine moiety is isolated as the brightly coloured dinitrodiphenylamine which crystallizes readily and is also suitable for chromatography on alumina. Thus by condensation with DNCB and subsequent hydrolysis two of the recently introduced Naphtols, AS-RS (C.I. Azoic coupling component 28) and AS-KN (C.I. Azoic coupling component 37) have been found to be constituted as VIII and IX. The former is highly substantive to cellulose and gives fast red shades with suitable diazonium salts; the latter gives dark grey to dark brown shades.



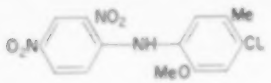
VIII



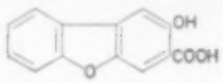
IX

Naphtol AS-RS, $C_{19}H_{16}O_3NCl$, contains a methoxyl group. Hydrolysis of the dinitrophenyl derivative gave 2-hydroxy-3-naphthoic acid and the N-dinitrophenyl derivative (X) of 3-amino-4-methoxy-6-chlorotoluene (chlorocresidine), from which the constitution of VIII followed and was confirmed by synthesis. Similarly the dinitrophenyl derivative of Naphtol AS-KN gave on hydrolysis 3-hydroxydibenzofuran-2-carboxylic acid (XI) and N-2,4-dinitrophenyl-α-naphthylamine; (XI) was identified by comparison with the acid obtained in a similar manner from Naphtol AS-BT (C.I. 37605), which is known to be the 2,5-dimethoxyanilide of XI.

* In this case the formation of *o*-dinitrophenyl derivative should be rate-determining since the second step involving the Smiles rearrangement is known to be very fast.



X



XI

EXPERIMENTAL

N-(2′,4′-Dinitrophenyl)-2-hydroxy-3-naphthanilide (III)

(a) A solution of 2-hydroxy-3-naphthanilide (1 g) in ethanol (50 ml) and 10% NaOH (1·5 ml) was added in 15 min to a stirred solution of DNFB (1 g) in ethanol (20 ml) at 50°. After stirring for 2 hr at 50–55°, the solution was poured into water (100 ml) and left overnight. The yellow precipitate crystallized from ethanol (Norit) in pale yellow plates (1·3 g), m.p. 183°, raised to 194° after 3 crystallizations. (Found: C, 64·8; H, 3·8; N, 9·6. $C_{23}H_{15}O_6N_3$ requires: C, 64·3; H, 3·5; N, 9·8%).

(b) When the above reaction was carried out with DNCB (1·2 g) for 3 hr at 65–70°, the product (0·9 g) melted at 194° after one crystallization. A slightly better yield was obtained by shaking the mixture at 35° for 18 hr.

(c) A solution of 2-hydroxy-3-naphthanilide (5 g) in DMF (50 ml) was shaken with DNCB (5 g) and triethylamine (3 ml) for 24 hr at 25° and then poured into water (400 ml). Crystallization of the precipitate successively from chlorobenzene and benzene–hexane gave yellow plates (5·2 g), m.p. 194°.

(d) 2-Hydroxy-3-naphthanilide (1·3 g), DNCB (1·1 g) and anhydrous potassium carbonate (0·35 g) were refluxed in methyl ethyl ketone (100 ml) for 17 hr. The solvent was distilled off, and the residue treated with water. The brownish red solid crystallized from ethanol in pale yellow plates (0·81 g), m.p. 194°.

N-(2′,4′-Dinitrophenyl)-salicylanilide (II)

(a) A solution of salicylanilide (0·84 g) in ethanol (25 ml) and 10% NaOH (1·6 ml) was refluxed with DNCB (1 g) for 3 hr. Dilution with water and ether extraction led to an oil, which was obtained crystalline from ethanol–acetone by slow cooling. The yellow needles (0·55 g) shrank at 75° and melted at 145°. (Found: C, 59·7; H, 4·0; N, 10·3. $C_{19}H_{12}O_6N_2$, C_2H_5OH requires: C, 59·3; H, 4·5; N, 9·9%).

(b) A solution of salicylanilide (2·1 g), DNFB (1·2 ml) and triethylamine (1·5 ml) in DMF (10 ml) was shaken at 25° for 24 hr and then poured into water (100 ml). The precipitate crystallized from benzene–hexane (Norit) in pale yellow prisms (1·2 g), m.p. 145°.

(c) When DNFB was replaced by DNCB (2·2 g) in (b), the yield of II was 2·25 g.

(d) To a refluxing solution of salicylanilide (1·06 g) and sodium bicarbonate (0·42 g) in ethanol (25 ml) a solution of DNCB (1·04 g) in ethanol (50 ml) was added over 15 min, and refluxing continued for 3 hr. The solution was poured into water (250 ml) and made slightly acidic with conc HCl. The solution was extracted with ether, and the oil obtained after removal of ether crystallized from ethanol in yellow needles (0·78 g), m.p. 145°, after shrinking at 76°.

(e) Salicylanilide (0·852 g), DNCB (0·81 g) and anhydrous potassium carbonate (0·14 g) were refluxed in acetone (50 ml) for 4 hr and poured into water (200 ml). Worked up as above, the yield was 0·72 g.

p-(2′,4′-Dinitrophenoxy)-benzanilide

p-Hydroxybenzanilide (0·6 g), DNCB (0·7 g) and triethylamine (0·5 ml) were dissolved in DMF (10 ml) and shaken for 24 hr at 25°. The solution was poured into water (200 ml) and a few drops of conc HCl. The precipitate crystallized from acetone in colourless plates (0·78 g), m.p. 225°. (Found: C, 60·2; H, 3·1; N, 11·0. $C_{19}H_{12}O_6N_2$ requires: C, 60·2; H, 3·4; N, 11·1%).

o-(2,4-Dinitrophenoxy)-N-methylbenzanilide

N-Methylsalicylanilide (1·14 g), DNCB (1·14 g) and triethylamine (0·7 ml) were dissolved in DMF (20 ml) and shaken for 24 hr at 25–30°, poured into water (250 ml), and acidified with a few drops of conc HCl. The yellow precipitate crystallized from ethanol in pale yellow plates (0·8 g), m.p. 176°. (Found: C, 16·4; H, 3·7; N, 10·5. $C_{20}H_{15}O_6N_3$ requires: C, 61·1; H, 3·8; N, 10·7%).

Salicyl-2,4-dinitroanilide (I)

A solution of salicylamide (1·4 g) in ethanol (20 ml) and 10% NaOH (4 ml) was stirred with DNCB (2·5 g) at 70–75° for 3 hr. The yellow precipitate obtained on adding water (150 ml) crystallized from benzene in yellow needles (0·78 g), m.p. 213–214° (Tozer and Smiles, m.p. 213°). (Found: C, 51·6; H, 3·2; N, 14·0. Calc. for $C_{13}H_9O_6N_3$: C, 51·5; H, 3·0; N, 13·9%).

Relative rates of reaction of aniline, N-methylsalicylanilide, p-hydroxybenzanilide and salicylanilide with DNCB

(a) Aniline (0·186 g; 0·002 M,) DNCB (0·405 g; 0·002 M) and triethylamine (0·28 ml; 0·002 M) were heated in DMF (10 ml) for 1 hr at 65–66°, poured into water (50 ml), and acidified with conc HCl. The resulting solution was extracted with benzene, and the benzene solution chromatographed on alumina. The reddish yellow band was eluted with benzene and the solvent distilled off. The residue was taken up in ethanol (5 ml) and cooled to 0°. Red needles of 2,4-dinitrodiphenylamine (0·23 g), m.p. 158°, were obtained.

(b) N-Methylsalicylanilide (0·454 g; 0·002 M) was reacted with DNCB under similar conditions. Isolation of the product with ether and crystallization from ethanol by cooling to 0° gave pale yellow plates (0·104 g), m.p. 176°.

(c) *p*-Hydroxybenzanilide (0·852 g; 0·004 M) was condensed with molar proportions of DNCB and triethylamine as above, poured into water (50 ml), and acidified with dilute HNO_3. The precipitate was filtered off, washed with cold ethanol, and dried (0·512 g; m.p. 222°). The aqueous filtrate was extracted with ether and the chloride in the aqueous solution was estimated as AgCl (0·1807 g). The amount of AgCl obtained is somewhat less than that expected from the yield of *o*-dinitrophenyl derivative. Some silver chloride is lost in the course of the analysis due to peptization, perhaps caused by unreacted *p*-hydroxybenzanilide in aqueous solution.

(d) Carrying out the above experiment on salicylanilide (0·852 g), the amount of AgCl was 0·507 g. The N-2,4-dinitrophenyl derivative (0·910 g) was isolated after extraction of the acidified solution with ether and crystallization from ethanol cooled to 0°. The amount of AgCl corresponds to 88% reaction, whereas the N-dinitrophenyl derivative isolated was only 53%. The discrepancy arises partly from the solubility of the dinitrophenyl derivative in ethanol and partly from side reactions, which were indicated by a large number of bands observed when the mother liquor was concentrated, dissolved in benzene and chromatographed on Florex. In experiments (a), (b) and (c) the recovery of the products was nearly quantitative.

Hydrolysis of III

(a) A solution of (III; 0·5 g) in ethanol (5 ml), 10% NaOH (5 ml) and water (40 ml) was stirred at 75–80° for 3 hr. The orange precipitate crystallized from ethanol (Norit) in red needles (0·19 g), m.p. 158°, alone or mixed with 2,4-dinitrodiphenylamine. The filtrate was saturated with carbon dioxide, filtered again, acidified with HCl and cooled. The precipitate, after two crystallizations from aqueous ethanol (Norit) gave brownish plates (0·1 g), m.p. 219°, identified as 2-hydroxy-3-naphthoic acid.

(b) A mixture of III (0·5 g), ethanol (10 ml), water (40 ml) and sodium carbonate (5 g) was refluxed for 14 hr, and the hot solution filtered. The residue (0·23 g) crystallized from ethanol (Norit) in orange-red needles, m.p. 158°, identified as 2,4-dinitrodiphenylamine. From the aqueous filtrate 2-hydroxy-3-naphthoic acid (0·12 g) was recovered.

Naphtol AS–RS

The Naphtol, after removal of water-soluble material, crystallized from ethanol in pale brown needles, m.p. 206°. (Found: C, 66·9; H, 4·9; Cl, 10·8; N, 4·4. $C_{19}H_{16}O_3ClN$ requires: C, 66·8; H, 4·7; Cl, 10·4; N, 4·1%). An alcoholic solution gives an olive-green colour with ferric chloride. The dye obtained by coupling with diazotized aniline crystallized from glacial acetic acid in red needles, m.p. 268°. (Found: C, 67·7; H, 4·7; Cl, 8·1; N, 9·4. $C_{25}H_{20}O_3ClN_3$ requires: C, 67·3; H, 4·5; Cl, 8·0; N, 9·4%).

N-(2,4-*Dinitrophenyl*)-*Naphtol* AS–RS

Naphtol AS–RS (1·7 g) and DNCB (1·1 g) were dissolved in triethylamine (0·75 ml) and DMF (25 ml) and shaken at 25° for 24 hr. Dilution with water (250 ml) gave a precipitate which crystallized

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from benzene–hexane (Norit) in yellow plates (1·8 g). Recrystallization from ethanol gave yellow cubes, m.p. 199°. (Found: C, 59·4; H, 3·0; Cl, 6·5; N, 8·2; OMe, 6·2. $C_{21}H_{14}O_7ClN_5$ requires: C, 59·2; H, 3·5; Cl, 7·0; N, 8·3; OMe, 6·1%).

Hydrolysis of the DNP *derivative of Naphtol* AS–RS

(a) The derivative (0·5 g) was hydrolysed with aqueous NaOH as in the case of III. The acid (0·09 g) melted at 219°, gave a greenish blue colour with alcoholic ferric chloride, and did not depress the m.p. of 2-hydroxy-3-naphthoic acid. The alkali-insoluble orange compound (0·28 g) crystallized from benzene–hexane in red needles, m.p. 201°. (Found: C, 49·7; H, 3·3; Cl, 10·3; N, 12·5; OMe, 9·1. $C_{15}H_{12}O_4ClN_5$ requires: C, 50·0; H, 3·6; Cl, 10·5; N, 12·4; OMe, 9·2%).

Condensation of 6-*chlorocresidine with* DNCB

A solution of 6-chlorocresidine (0·54 g), DNCB (0·7 g) and triethylamine (0·5 ml) in DMF (5 ml) was shaken at 25° for 24 hr and then poured into water (100 ml). The red precipitate crystallized from benzene (Norit) in red needles (0·38 g), m.p. 201°, not depressed by mixing with the alkali-insoluble product of the hydrolysis of the DNP derivative of Naphtol AS–RS.

Condensation product (VII) *of* 6-*chlorocresidine with* 2-*hydroxy*-3-*naphthoyl chloride*

2-Hydroxy-3-naphthoyl chloride (0·3 g) and 6-chlorocresidine (0·2 g) were refluxed in pyridine (5 ml) for 3 hr and then poured into dilute HCl. The precipitate was filtered, washed with water and sodium bicarbonate solution, dried and crystallized from benzene (Norit). The yellow plates (0·22 g), m.p. 206°, did not depress the m.p. of Naphtol AS–RS.

Naphtol AS-KN

The Naphtol, thrice crystallized from DMF, was obtained as pale brown plates m.p. 304°. (Found: C, 78·3; H, 4.5; N, 4·0. $C_{28}H_{19}O_2N$ requires: C, 78·2; H, 4·2; N, 4·0%).

N-(2,4-*Dinitrophenyl*)-*Naphtol* AS–KN

Naphtol AS–KN (1·75 g), DNCB (1·1 g), triethylamine (0·75 ml) and DMF (25 ml) were shaken for 24 hr at 25°. The product (2·35 g), crystallized successively from benzene–hexane and chlorobenzene–petroleum ether (b.p. >120°), was obtained as yellow prisms, m.p. 170°. (Found: C, 67·0; H, 3·0; N, 7·6. $C_{28}H_{17}O_7N_5$ requires: C, 67·0; H, 3·3; N, 8·1%).

Hydrolysis of the DNP *derivative of Naphtol* AS–KN

The compound (1 g) was refluxed for 4 hr with ethanol (10 ml), 10% NaOH (10 ml) and water (80 ml). The alkali-insoluble product was taken up in benzene and chromatographed on alumina. The golden yellow band was eluted with benzene, concentrated, and diluted with a little hexane. Orange-red needles (0·26 g), m.p. 192°, were obtained. (Found: C, 61·8; H, 3·8; N, 13·7. Calc. for $C_{16}H_{11}O_4N_3$: C, 62·1; H, 3·6; N, 13·6%). This did not depress the m.p. of N-(2,4-dinitrophenyl)-α-naphthylamine. The alkaline filtrate obtained from the hydrolysis was saturated with carbon dioxide, filtered, acidified and extracted with ether. The ether extract yielded an acid (0·14 g), which crystallized from ethanol (Norit) in colourless needles, m.p. 293° (decomp). (Found: C, 68·5; H, 3·7. Calc. for $C_{12}H_8O_4$: C, 68·4; H, 3·5%). The alcoholic solution gives a reddish blue ferric colour.

N-(2,4-*Dinitrophenyl*)-*Naphtol* AS–BT

Naphtol AS–BT (1·8 g) was treated with DNCB (1·1 g), triethylamine (0·8 ml) and DMF (25 ml) under the usual conditions. The product crystallized from ethanol in yellow rods (1·74 g); crystallization from chlorobenzene-petroleum ether (b.p. >120°) gave yellow prisms, m.p. 137°. (Found: C, 61·8; H, 3·8; N, 7·4. $C_{22}H_{13}O_7N_5$ requires: C, 61·3; H, 3·6; N, 7·9%).

Hydrolysis of the DNP *derivative of Naphtol* AS–BT

The compound (2 g) was heated with ethanol (20 ml), 10% NaOH (20 ml) and water (160 ml) for 8 hr. The orange precipitate was filtered, and from the filtrate the acid was recovered as usual. It crystallized from ethanol in needles (0·24 g), m.p. 293° (decomp), not depressed by mixing with the acid component of Naphtol AS–KN. The alkali-insoluble orange product, after chromatography of

a chlorobenzene solution on alumina, crystallized from benzene in red needles (0·49 g), m.p. 188°. (Found: C, 52·8; H, 3·8; N, 12·9. $C_{14}H_{13}O_6N_3$ requires: C, 52·7; H, 4·1; N, 13·2%). The substance was identified as 2,4-dinitro-2′,5′-dimethoxydiphenylamine, prepared by condensing DNCB with 2,5-dimethoxyaniline.

Condensation of 3-hydroxydibenzofuran-2-carboxylic acid with α-naphthylamine

The acid (0·22 g) in chlorobenzene (20 ml) and DMF (1 ml) was heated on a water-bath with thionyl chloride (0·8 ml) for 15 min. To the clear solution α-naphthylamine (0·14 g) in chlorobenzene (10 ml) and pyridine (2 ml) was added, and heating continued for 45 min. Chlorobenzene was steam-distilled, and the residue washed with sodium carbonate solution and a little methanol. Crystallization from cellosolve gave plates, m.p. 304°, not depressed by mixing with Naphtol AS–KN (DRP 607,381 quotes m.p. of 295° for this compound).

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A DEGRADATION OF GELSEMINE

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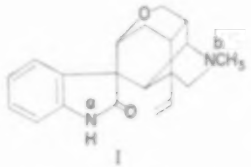
Abstract—An unusual reversible degradation of a quaternary gelsemine derivative is described.

THE structure of gelsemine (I), one of the main alkaloids of *Gelsemium sempervirens* has recently been ascertained by x-ray crystallographic means by Pepinsky *et al.*[2] and the degradative studies and biogenetic considerations of Conroy and Chakrabarti[3] published at the same time are in full agreement with this structure, independently deduced by them.



I

Conroy's degradative studies are especially noteworthy in that they describe for the first time a method by which the highly compact cage structure containing N(b) can be breached. The many earlier degradative studies[4] had utterly failed to open this system and in particular had demonstrated that no quaternary derivatives of this system will undergo a normal Hofmann elimination.

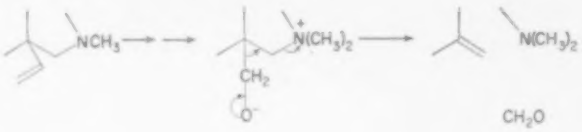
Thus, gelsemine and dihydrogelsemine methohydroxides on attempted Hofmann degradation yield N(a)-methylgelsemine and N(a)-methyldihydrogelsemine respectively,[5] and the methohydroxides of these N(a)-methyl derivatives when heated merely return the corresponding tertiary bases with loss of methanol.[5]

These results are readily understandable on the Pepinsky–Conroy structure since both hydrogen atoms β to N(b) are at bridgehead positions which cannot accommodate a double bond.

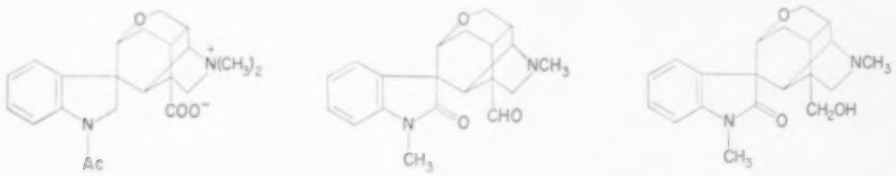
At the time our work was undertaken the structure of gelsemine was unknown, but there were strong biogenetic reasons for believing that the vinyl group was

[1] Geschickter Foundation Postdoctoral Fellow. Present address: Smith Kline and French Research Institute, Welwyn Garden City, Herts., England.
[2] F. M. Lovell, R. Pepinsky and A. J. C. Wilson, *Tetrahedron Letters* No. 4, 1 (1959).
[3] H. Conroy and J. K. Chakrabarti, *Tetrahedron Letters* No. 4, 6 (1959).
[4] These studies had indicated the presence of the 3,3-disubstituted oxindole system, a tertiary nitrogen carrying a methyl group in a 5 membered ring, a vinyl group, an inert oxygen atom in a system containing six rings, and had indicated the proximity of the oxindole oxygen and the vinyl group. cf. *inter alia*, L. Marion, *Canad. J. Res.* **B21**, 247 (1943); M. Kates and L. Marion, *J. Amer. Chem. Soc.* **72**, 2308 (1950); L. Marion, *Canad. J. Chem.* **29**, 37 (1951); R. Goutarel, M. M. Janot, V. Prelog, R. P. A. Sneeden and W. I. Taylor, *Helv. Chim. Acta* **34**, 1139 (1951); G. Jones and T. S. Stevens, *J. Chem. Soc.* 2344 (1953); T. Habgood and L. Marion, *Canad. J. Chem.* **33**, 604 (1955); L. Marion and K. Sargeant, *J. Amer. Chem. Soc.* **78**, 5127 (1956); *Canad J. Chem.* **35**, 301 (1957).
[5] R. Goutarel, M. M. Janot, V. Prelog and R. P. A. Sneeden, *Helv. Chim. Acta* **34**, 1962 (1951); T. Habgood, L. Marion and H. Schwarz, *Ibid.* **35**, 638 (1952); V. Prelog, J. B. Patrick and B. Witkop, *Ibid.* **35**, 640 (1952). The methohydroxide of N(a)-methyl-nor-gelsemine aldehyde (IV) also loses methanol on pyrolysis, yielding the tertiary aldehyde; *vide infra*.

attached to a carbon atom which stood β to N(b). In this circumstance it should be possible to effect a degradation of the following type:



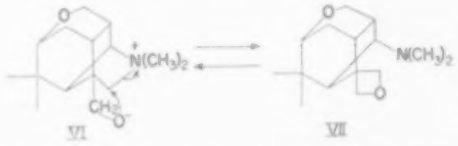
Reactions of this sort have been observed in simple systems,[6] particularly when the β carbon atom is disubstituted, and the reaction is similar in principle to the successful degradation carried out by Conroy[3] on the related betaine III, whose decarboxylation is accompanied by a ring opening of this type.



We accordingly undertook a study of the thermal degradation of the methohydroxide of N(a)-methyl-nor-gelsemine carbinol (V), prepared by borohydride reduction[7] and methylation of Marion's N(a)-methyl-nor-gelsemine aldehyde (IV).[8]

The results obtained were unexpected, and while they do not add to the structural conclusions already available, they are consistent with the structural proposals of Pepinsky and of Conroy and seem to be of sufficient intrinsic chemical interest to report.

When the crystalline N(a)-methylgelsemine-nor-carbinol methohydroxide trihydrate[9] is heated under reduced pressure, no formaldehyde is formed, but a highly fugitive anhydro-base which we formulate as the 3,3-spirotrimethylene oxide derivative VII sublimes in nearly quantitative yield. Analysis immediately after sublimation gives values corresponding to $C_{21}H_{26}O_3N_2$; after several days the



[6] V. J. Traynelis and J. G. Dadura, Abstracts of Papers presented at the 134th Meeting of the American Chemical Society, Chicago (1958).

[7] This carbinol also results from the action of ethanolic potassium hydroxide on N(a)-methyl-nor-gelsemine aldehyde IV (cf. Experimental) by way of either a reaction of the Cannizzaro type or a Meerwein–Ponndorf–Verley reduction. This is strong presumptive evidence that the carbon atom α to the aldehyde carbonyl does not bear a hydrogen atom and to this extent confirms Conroy's conclusion based on the NMR spectrum of N(a)-acetyldeoxo-nor-gelsemine aldehyde.

[8] L. Marion and K. Sargeant, *Canad. J. Chem.* 35, 301 (1957).

[9] The corresponding methiodide, from which this substance is produced by ion exchange, can be obtained in 55% yield by preparation of N(a)-methylgelsemine methiodide in one step followed by oxidative cleavage and borohydride reduction of the aldehyde in another step. (cf. Experimental).

analytical results indicate that water is being taken up by the sublimate. This formulation is strongly supported by the NMR spectrum of the substance. In Table 1 the gross features of its spectrum and that of dihydrogelsemine are compared. The appearance of a group of poorly resolved peaks corresponding to approximately 4 protons in the range 5·1 to 5·5 τ and a completely unsplit peak at 8·0 τ corresponding

TABLE 1. NMR SPECTRA[a] OF ANHYDRO SUBLIMATE (VII) AND DIHYDROGELSEMINE. RELATIVE INTEGRATED AREAS AND PROBABLE ASSIGNMENTS

Proton	τ[b]	Anhydro-base (VII)		Dihydrogelsemine[c]	
		observed	calc	observed	calc
N(a) H	<2·0	0	0	1	1
Aryl H—	2·3–3·7	4	4	4	4
—O—CH_2—C— (trimethylene oxide)	5·1–5·5	3–4	4	0	0
O—CH— (ether)	5·9	4–5	1	1	1
O—CH_2— (ether)	6·1		2	2	2
N(b) CH—	6·6–6·7		1	1	1
N(a) CH_3	6·9	3[d]	3	0	0
N(b) CH_2—	6·9–7·6		0	3	2
C—CH	7·9–8·2	5	3	6	3
C—CH_2	7·9–8·2		2		4
N(b) CH_3	7·8–8·0	6[d]	6	3[d]	3
C—CH_3	9·2	0	0	3[e]	3
			26		24

[a] Determined at 60 mc in deuterochloroform (conc approx 20%) with tetramethylsilane and chloroform as internal standards.

[b] Chemical shifts in p.p.m. relative to tetramethylsilane = 10. cf. G. V. D. Tiers, *J. Phys. Chem.* **62**, 1151 (1958).

[c] The NMR spectrum of dihydrogelsemine has been reproduced in part and discussed in, J. A. Pople, W. G. Schneider and H. J. Bernstein, *High Resolution Nuclear Magnetic Resonance* p. 281. McGraw-Hill (1959).

[d] Singlet

[e] Triplet

to 6 protons, the first assigned to the four non-equivalent hydrogens of the trimethylene oxide ring,[10] the second to two equivalent tertiary N-methyl groups,[11] is decisive.

The infrared spectrum of the sublimate also supports its formulation as VII. According to Barrow and Searles[12] the trimethylene oxide ring shows intense absorption at about 8·0 μ and at 10·2–10·3 μ, but the absence of absorption in the

[10] NMR absorption at 5·81 τ and 5·64 τ has been observed for the ring methylene hydrogens of 3,3-diethyltrimethylene oxide (private communication from S. Searles) and of 3,3-dichloromethyltrimethylene oxide (private communication from G. V. D. Tiers) respectively. The ring methylene hydrogens adjacent to oxygen in 1-oxa[4 . 2 . 0] bicyclooctane (τ = 5·54) and in 1-oxa-5-methyl[2 . 2 . 0] bicyclohexane (τ = 5·13, 5·61) also fall in this range (private communications from D. S. Tarbell and A. Rosowsky and from R. Srinivasan).

[11] In the starting quaternary carbinol hydroxide the two unsplit peaks corresponding to these two (non-equivalent in this case) N—CH_3 groups occur at 7·08 and 7·17 τ. Among the calabash curare alkaloids quaternary N—CH_3 groups also occur in this region (6·8–7·0 τ), 0·7–0·8 p.p.m. less than the corresponding tertiary N—CH_3 resonance. (Private communication from V. Boekelheide and O. Ceder.)

[12] G. M. Barrow and S. Searles, *J. Amer. Chem. Soc.* **75**, 1175 (1953).

8·0 μ region in some trimethylene oxides has been noted by Campbell[13]. A comparison of the infrared absorption in this region of several 3,3-disubstituted trimethylene oxide derivatives and of our anhydro-base is given in Table 2.

Perhaps the most striking feature of the chemistry of the anhydro-base VII is the great ease with which the reaction by which it is formed is reversed. When freshly sublimed, it is readily soluble in non-polar solvents such as benzene, ether, methyl

TABLE 2. SELECTED INFRARED ABSORPTION BANDS

3,3-Dimethyl trimethylene oxide[13a]	Bis-3,3-chloromethyl trimethylene oxide[13a]	Bis-3,3-bromomethyl trimethylene oxide[13b]	Bis-3,3-aminomethyl trimethylene oxide[13b] dihydrobromide	Anhydro-base (VII)[c]
8·05[d]	8·1	—	—	8·03
10·15	10·15	10·20	10·45	10·30
10·6	10·45	10·57	10·68	10·53

[a] Liquid sample
[b] Potassium bromide pellet or chloroform solution
[c] Potassium bromide pellet
[d] Microns

iodide, chloroform and the like as well as in simple alcohols, but its chloroform solution on standing deposits N(a)-methyl-nor-gelsemine carbinol methohydroxide trihydrate in crystalline form. When dissolved in 50 per cent aqueous ethanol, the anhydro-base exhibits an initial pH of 6·9, but this rises to pH 12·3 in about half a minute,[14] and from such solutions the crystalline methohydroxide trihydrate can be isolated. The tendency of VII to revert to the quaternary alkoxide VI is in fact so great that attempts to stabilize the opened form VII by quaternization (with methyl iodide) so that further degradations could be carried out on it have uniformly given only N(a)-methyl-nor-gelsemine carbinol methiodide.

It may be remarked in passing that the reaction by which VII is formed from VI is merely the intramolecular counter-part of the reaction by which other quaternary hydroxides in this series return to the corresponding tertiary bases with loss of methanol, i.e. the nucleophilic attack of alkoxide (or hydroxide) on a carbon atom α to the quaternary nitrogen. Both this reaction and its reverse appear to be examples of reactions which are enormously facilitated by the proximity imposed on the reacting centers by the rigid geometry of this system.

EXPERIMENTAL[15]

N(a)-*Methyl-nor-gelsemine carbinol* (V). A solution of 425 mg N(a)-methyl-nor-gelsemine aldehyde (IV),[a] m.p. 197–200°, in 20 ml 50% aqueous methanol was treated with 400 mg sodium borohydride in portions. The solution was warmed gently for a few min, and after 1 hr the excess reagent was destroyed by the addition of dil acetic acid. The solution was made basic with ammonia and extracted with chloroform and the extracts were washed, dried and concentrated to yield a colorless residue which crystallized readily from benzene as colorless prisms, 378 mg, m.p. 243–250°. A second

[13] T. W. Campbell, *J. Org. Chem.* **22**, 1029 (1957).
[14] Compare the similar rise in basicity which occurs during the reconversion of the anhydro-base from tetrahydroberberine (or l-canadine) methohydroxide to this quaternary hydroxide. cf. F. L. Pyman, *J. Chem. Soc.* **103**, 821 (1913).
[15] Melting points are uncorrected. Analyses were done by W. Manser, Zurich and Microtech Laboratories.

crop had m.p. 242–247·5°. Recrystallization from benzene raised the m.p. to 249–250°. (Found: C, 70·56; H, 7·08; N, 8·12. $C_{20}H_{24}O_3N_2$ requires: C, 70·56; H, 7·11; N, 8·23%).

The same substance resulted when the aldehyde IV (60 mg) was heated under reflux for 13 hr with a solution of 1·2 g potassium hydroxide in 6 ml ethanol. Dilution with water and extraction with chloroform yielded after concentration a pale orange oil (50 mg) which solidified under ether and whose infrared spectrum was indistinguishable from that of the sample described above.

N(a)-*Methyl*-nor-*gelsemine carbinol methiodide*. This was prepared in and crystallized from ethanol, colorless needles, m.p. 288–290° (dec). Highly purified samples occasionally melt as high as 304–305° (dec). (Found: C, 52·06; H, 6·03; N, 5·48; I, 25·20. $C_{21}H_{27}O_3N_2I$ requires: C, 52·28; H, 5·65; N, 5·81; I, 26·32%) $[\alpha]_D^{22} = +16°$ (*c* 1·05, water).

This methiodide can also and more conveniently be prepared directly from gelsemine as follows: A solution of 5·00 g of the acetone solvate of gelsemine in 140 ml reagent grade toluene was concentrated to about 100 ml by boiling to remove acetone and traces of water, cooled, and treated with 726 mg of a 49·6% dispersion of sodium hydride in mineral oil. After the immediate copious gas evolution had ceased, the mixture was heated under reflux for 2 hr, allowed to cool, treated with 4 ml methyl iodide, and refluxed for 30 min. More methyl iodide (5 ml) was added and the mixture allowed to stand at room temp for several days. The colorless crystalline solid, crude N(a)-methyl-gelsemine methiodide, was collected, washed with benzene, dried (8·88 g) and converted to the chloride by ion exchange over 70 g Dowex 2-x4 (chloride form) in 50% aqueous methanol. The resulting solution was concentrated under diminished pressure to yield the crude quaternary chloride as a yellow gum which in contrast to the iodide was readily soluble in methanol. Filtration of its solution in this solvent removed 0·61 g sodium chloride, and the resulting clear solution was concentrated to yield 5·69 g (theory 5·08 g) of the chloride. A solution of this substance in 85 ml water was treated with 150 mg osmium tetroxide with stirring. A chocolate brown color was produced, and after 10 min a solution of 5·90 g sodium meta periodate in the minimum amount of water was added dropwise. The brown but essentially homogeneous solution was allowed to stand 1 hr, then warmed on the steam bath for 20 min, during which it lightened to pale yellow, finally allowed to cool and treated with 2 g sodium borohydride. Much gas was evolved and a fine black precipitate of osmium dioxide was produced. After standing overnight the solution was filtered, concentrated to about 50 ml under diminished pressure (crystalline precipitate) and treated with 2·0 g sodium iodide. Crude crystalline N(a)-methyl-nor-gelsemine carbinol methiodide, 5·20 g (theory 6·31), m.p. 278–280° (dec), was obtained. Recrystallization from alcohol–water gave 3·47 g (55%) of material of acceptable quality, m.p. 279–286° (dec).

N(a)-*Methyl*-nor-*gelsemine carbinol methochloride*. This was prepared from the iodide (or the hydroxide) by ion exchange on Dowex 2-x4, m.p. 294–295° (dec) when crystallized from absolute ethanol–ether. (Found: (on sample dried at 100° *in vacuo*) C, 62·78; H, 7·11; N, 6·99. $C_{21}H_{27}O_3N_2Cl \cdot \frac{1}{2}H_2O$ requires: C, 63·05; H, 7·06; N, 7·00%)

N(a)-*Methyl*-nor-*gelsemine carbinol methohydroxide*. This was prepared from the iodide by ion exchange on Dowex 2-x4 (hydroxide form) and crystallized from 95% alcohol–ether, fine needles, m.p. 296–297° (dec). (Found: (on air-dried sample) C, 59·05; H, 8·14; N, 6·55; H_2O, 4·22, 4·39 (loss in wt. on drying at 100°). $C_{21}H_{28}O_4N_2 \cdot 3H_2O$ requires: C, 59·13; H, 8·04; N, 6·57; H_2O (loss of 1 H_2O) 4·23%) uv λ_{max} 254 mμ (log ε 3·8), 284 mμ (shoulder) (log ε 3·1), $[\alpha]_D^{22} = +16°$ (*c* 0·88, water).

The O-*acetyl derivative of* N(a)-*methyl*-nor-*gelsemine carbinol methiodide*. This was prepared by heating a solution of 105 mg of the methiodide in 2 ml acetic anhydride to reflux for 30 min. The cooled solution was diluted with methanol, allowed to stand for a few min, then concentrated to dryness under diminished pressure. The colorless residue was dissolved in hot water, treated with sodium iodide and allowed to crystallize, small prisms, 51 mg, m.p. 260–265° (dec). Recrystallization from water raised the m.p. to 265–270° (dec). IR max *inter alia* 5·82, 5·88 and 7·98 μ (O-acetyl group and N(a)-methyl oxindole carbonyl). (Found: C, 51·71; H, 5·71. $C_{23}H_{29}O_4N_2I \cdot \frac{1}{2}H_2O$ requires: C, 51·79; H, 5·67%).

Pyrolysis of N(a)-*methyl*-nor-*gelsemine carbinol methohydroxide. The anhydro-base* VII. When this methohydroxide (48 mg) was heated in a stream of nitrogen at temp ranging from 150–190°, extensive decomposition took place. The nitrogen stream was passed into 2 N hydrochloric acid saturated with 2,4-dinitrophenylhydrazine, but no formaldehyde 2,4-dinitrophenylhydrazone was detected. Sublimation of the residue at 10^{-4} mm and 150–200° afforded a sublimate (5 mg) whose infrared spectrum was identical with that of N(a)-methyl-nor-gelsemine carbinol.

When, however, N(a)-methyl-nor-gelsemine carbinol methohydroxide trihydrate (205 mg) was sublimed at 160–170° and 10^{-4} mm, a colorless sublimate was produced, and an inappreciable residue (2 mg) remained. Analysis of a sample of sublimate prepared in this way immediately after sublimation (Found: C, 71·40; H, 7·73. $C_{21}H_{26}O_3N$ requires: C, 71·17; H, 7·39%) indicates that an anhydro-base has been produced. Analysis after a week or so suggests that water is being absorbed (Found: C, 70·24; H, 7·89; N, 7·69%). The sublimate is readily soluble in benzene, chloroform, ether, acetone and ethanol but insoluble in water. When a portion of the sublimate was dissolved in 50% aqueous ethanol, the pH as determined by a glass electrode increased from 6·9 to 12·3 in about ½ min. A solution of the sublimate in chloroform deposited on standing crystalline material whose infrared spectrum was indistinguishable from that of the starting N(a)-methyl-nor-gelsemine carbinol methohydroxide trihydrate, which contained no iodide ion, whose solution in water had pH ca. 12 and whose electrophoretic mobility was the same as quaternary salts in this series.

Attempted quaternization of the anhydro-base VII *with methyl iodide.* The sublimate (10^{-3} mm, 160–170°) from 345 mg N(a)-methyl-nor-gelsemine carbinol methohydroxide trihydrate (residue 4·2 mg) was taken into methyl iodide and allowed to stand 1 day. Removal of the methyl iodide and examination of the infrared spectrum of the residue showed that the residue was essentially unchanged sublimate, so the residue was warmed with methyl iodide in acetonitrile. The solvents were removed, and the residue yielded 247 mg of material soluble in chloroform, which, when passed in methanol through an ion exchange column (Dowex 2-x4) in the iodide form, yielded N(a)-methyl-nor-gelsemine carbinol methiodide, m.p. 282–284° (dec), not depressed by admixture of authentic methiodide. Their infrared spectra were indistinguishable.

Attempted Hofmann degradation of N(a)-*methyl*-nor-*gelsemine aldehyde methohydroxide.* N(a)-Methyl-nor-gelsemine aldehyde methiodide (16 mg), prepared from the aldehyde in the usual way and crystallized from acetone–ether, m.p. 255–265° (variable with dec). (Found: C, 52·37; H, 5·46; N, 5·23. $C_{21}H_{25}O_3N_2I$ requires: C, 52·51; H, 5·25; N, 5·84%) was converted to the hydroxide in methanol over Dowex 2-x4 (hydroxide form), and the residue remaining after removal of the solvent was sublimed (at 170–180° and 2×10^{-4} mm). The infrared spectrum of the pale yellow sublimate (10 mg) was indistinguishable from that of N(a)-methyl-nor-gelsemine aldehyde.

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EXPERIMENTS IN THE 4-ARYLCYCLOALK-2-EN-1-ONE SERIES—IV[1]

4-PHENYLCYCLOHEPTA-1,3-DIONE

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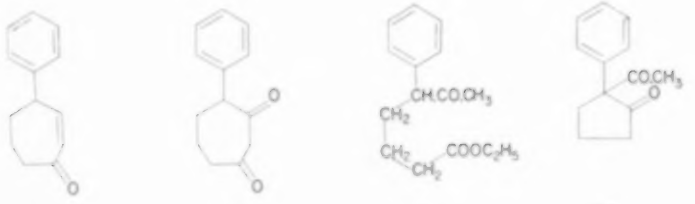
(*Received* 25 *June* 1960)

Abstract—4-Phenylcyclohepta-1,3-dione (II) and 2-acetyl-2-phenylcyclopentanone (IV) have been prepared and their properties studied.

IN continuation of previous attempts to synthetize 4-phenylcyclohept-2-en-1-one (I), the synthesis of 4-phenylcyclohepta-1,3-dione (II) was undertaken, in the hope that this might conveniently be transformed into I. The synthesis of II was modeled on that of the lower homolog 4-phenylcyclohexa-1,3-dione[2] and started from the same point of departure, *viz* phenylacetone. The four additional carbon atoms were introduced by means of ethyl γ-iodobutyrate. The use of sodium hydroxide,[3] sodium ethoxide[4] and sodium isopropoxide[5] was unsatisfactory, but with sodium hydride in a mixture of benzene and dimethylformamide,[6] the desired ethyl 6-oxo-5-phenylheptoate (III) was obtained in 60 per cent yield. In its cyclization, the ester group can *a priori* attack either side of the ketone carbonyl. In fact, both reactions took place, and a mixture of equal parts of 4-phenylcyclohepta-1,3-dione (II) and 2-acetyl-2-phenylcyclopentanone (IV) was obtained.



I II III IV

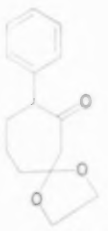
Surprisingly, neither II nor IV reacted with the usual ketone reagents. Their structures, however, are supported by their behaviour and their spectra. The former gives a vivid colour reaction with ferric chloride and is strongly acidic, the latter is refractory in both respects. Compound II forms a very stable hydrate and in the infra-red spectrum, exhibits a very intense hydroxyl band; its width (2800–3200 cm^{-1}) recalls

[1] Part III: E. D. Bergmann and S. Yaroslavsky, *J. Amer. Chem. Soc.* **81**, 2772 (1959).
[2] E. D. Bergmann and J. Szmuszkovicz, *J. Amer. Chem. Soc.* **75**, 3226 (1953).
[3] E. M. Schultz, J. B. Bicking, S. Mickey and F. S. Crossley, *J. Amer. Chem. Soc.* **75**, 1072 (1953).
[4] M. Tiffeneau and L. Levy, *Bull. Soc. Chim.* [4], **33**, 759 (1923).
[5] C. M. Suter and A. W. Westeon, *J. Amer. Chem. Soc.* **64**, 533 (1942).
[6] F. J. Marshall and W. N. Cannon, *J. Org. Chem.* **21**, 245 (1956).

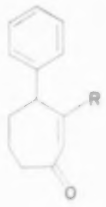
the absorption of a carboxylic hydroxyl group; indeed, the enol form of II is a vinylogous carboxylic acid. For II, the ultra-violet spectrum in ethyl alcohol shows two maxima 251 mμ (3·43); 289 mμ (3·12), which is indicative of alicyclic 1,3-diketones[7] and has been explained by Blout *et al.*[8]

For synthetic experiments, e.g. the Stobbe reaction, the monoketal of II appeared to offer possibilities. The monoketalization was attempted in the manner which had proved successful for cyclohexa-1,3-dione[9] and in the expectation that the less hindered carbonyl would react preferentially, giving V. In fact, no ketalization took place; the product obtained was either the β-hydroxyethyl ether VI or VII, which are derived from the two enolic forms of II, the latter reacting like a carboxyl group yielding the ester, or a mixture of both. The analysis conformed with the formula (as monohydrate), and the infra-red spectrum revealed the presence of an alcoholic hydroxyl group (3450 cm^{-1}) in addition to the carbonyl band.

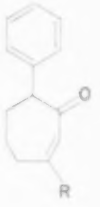
The diketone (II) was, therefore, converted into its enol monoethyl ether, probably the mixture of the two isomers VIII and IX. These enol ethers, too, give fairly stable monohydrates.[10] Their absorption spectrum showed a maximum at 250 mμ (3·43), exactly, as the corresponding cyclohexane derivatives.[2]



V



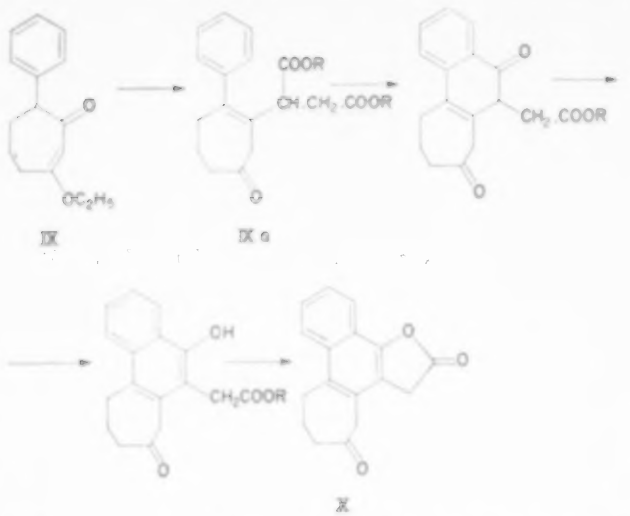
VI R=OCH_2CH_2CH
VIII R=OC_2H_5



VII R=OCH_2CH_2OH
IX R=OC_2H_5

The Stobbe reaction with the mixture of the enol ethers VIII and IX produced an oily acidic product, which could not be characterized as such, but gave upon treatment with polyphosphoric acid, in 20 per cent yield, a crystalline neutral material of the composition $C_{17}H_{14}O_3$. The compound showed two infra-red absorption bands in the carbonyl region, at 1687 and at 1823 cm^{-1}. The former represents a seven-membered ring carbonyl,[11] the latter indicates the presence of a β,γ-unsaturated γ-lactone.[12] Formula X is proposed for this compound. It would be formed from IX by the following route (see top of page 156). The Stobbe product (IX A) has the structure of a substituted 3-benzylidenepropionic acid and is thus capable of undergoing the classical α-naphthol synthesis of Fittig and Erdmann[13]; the product, as a derivative of the unstable *o*-hydroxyphenylacetic acid,

[7] H. Bastron, R. E. Davis and L. W. Butz, *J. Org. Chem.* **8**, 522 (1943).
[8] E. R. Blout, V. W. Eager and D. C. Silverman, *J. Amer. Chem. Soc.* **68**, 566 (1946).
[9] M. W. Cronyn and J. E. Goodrich, *J. Amer. Chem. Soc.* **74**, 3331 (1952).
[10] The analytical figures given by Bergmann and Szmuszkovicz[2] for the analogous monoethyl ethers derived from 4-phenylcyclohexa-1,3-dione also point to the existence of monohydrates of these compounds.
[11] C. D. Gutsche, *J. Amer. Chem. Soc.* **71**, 3513 (1949) found the carbonyl peak for 2- and 3-phenylcycloheptanone at 1688 cm^{-1}, whilst 4-phenylcycloheptanone[1] absorbs at 1700 cm^{-1}.
[12] J. F. Grove and H. A. Willis, *J. Chem. Soc.* 877 (1951); R. S. Rasmussen and R. R. Brattain, *J. Amer. Chem. Soc.* **71**, 1073 (1949).
[13] R. Fittig and H. Erdmann, *Ber. Dtsch. Chem. Ges.* **16**, 43 (1883); *Liebigs Ann.* **227**, 242 (1885).



IX IX a X

forms immediately a coumaran-2-one (X).[14] This mechanism is supported by a number of analogous observations made on products from Stobbe reactions with substituted benzyl ketones (IX also belongs to this class). These observations are reported in the following paper.

EXPERIMENTAL

Ethyl γ-bromobutyrate.[15] A mixture of 250 g γ-butyrolactone, saturated with gaseous hydrogen bromide, with benzene and absolute ethanol was subjected to azeotropic distillation. When no more water appeared in the trap, the benzene solution was cooled, washed with sodium carbonate and water, and dried over magnesium sulphate. Distillation yielded 500 g (90%) of ethyl γ-bromobutyrate, b.p. 98–100°/20 mm.

Ethyl γ-iodobutyrate.[15] A mixture of 288 g sodium iodide, 280 g ethyl γ-bromobutyrate and 1200 ml acetone was shaken for 4 hr. After filtration, the acetone was distilled off and the residue taken up in benzene. The benzene layer was washed several times with sodium bisulphite solution and water, dried and distilled. Thus, 319 g (92%) ethyl γ-iodobutyrate, b.p. 100–101°/20 mm, was obtained.

Ethyl 6-oxo-5-phenylheptoate (III). To a well-stirred mixture of 14·3 g (0·6 mole) sodium hydride, 222 ml dry benzene and 222 ml anhydrous dimethylformamide, 80 g (0·6 mole) phenylacetone was added dropwise during 20 min at 5–10°. The beginning of the reaction is indicated by foam formation. If this does not occur, the mixture is gently heated before continuing the addition of phenylacetone. After the addition, the stirring was continued for 20 min and 157 g (0·65 mole) ethyl γ-iodobutyrate added dropwise at 10°. The reaction mixture was allowed to reach room temp and then heated at 50–60° for 5 hr. After cooling, 20 ml ethanol, and then water, was added, and the benzene layer washed with sodium bisulphite and water. Distillation yielded 20 g (35%) phenylacetone, b.p. 108°/20 mm, and 87 g (60%) III, b.p. 135°/1 mm λ_{max}^{EtOH} 220 (3·87), 260 (2·53), 284 mμ (2·47) $\bar{\nu}_{C=O\,max}^{KBr}$ 1711, 1733 cm^{-1}. (Found: C, 72·3; H, 7·6. $C_{15}H_{20}O_3$ requires: C, 72·6; H, 8·0%). The ester (III) gave an orange-yellow 2,4-dinitrophenylhydrazone which was recrystallized from ethanol, m.p. 78°.

4-Phenylcyclohepta-1,3-dione (II). To a stirred solution of sodium ethoxide in boiling ethanol (from 8·54 g sodium and 200 ml absolute ethanol), 91 g III was added dropwise. The heating was

[14] A. v. Baeyer and P. Fritsch, *Ber Dtsch Chem Ges.* **17**, 973 (1884).
[15] D. J. Cram and H. Steinberg, *J. Amer Chem. Soc.* **76**, 2753 (1954); G. D. Johnson, W. B. Lindsey and B. R. Jones, *J. Amer. Chem. Soc.* **78**, 461 (1956).
[16] R. C. Fuson, R. T. Arnold and H. G. Cooke, *J. Amer. Chem. Soc.* **60**, 2272 (1938); N. J. Leonard, R. C. Fox and M. Oki, *Ibid.* **76**, 5708 (1954).

continued for 2 hr and the mixture, after cooling, acidified by 30 ml acetic acid followed by water. The product was extracted with ether and the *acidic product* transferred into sodium carbonate solution (5%). Acidification with cold dil. sulphuric acid (5%) gave an oil which was extracted again with ether and washed with sodium chloride solution. Distillation yielded 36 g (50%) 4-phenylcyclohepta-1,3-dione (II), b.p. 180°/1 mm. The product gave a deep-violet colour reaction with ethanolic ferric chloride and did not react with 2,4-dinitrophenylhydrazine or semicarbazide. It holds tenaciously about one molecule of water; therefore, its analysis is not altogether satisfactory. λ_{max}^{EtOH} 251 (3·43); 289 mμ (3·12). $\tilde{\nu}_{max}^{liq}$ 1700 (shoulders at 1714 and 1724 cm^{-1}); 2800–3200 cm^{-1} (hydroxyl). (Found: C, 72·1; H, 7·3. $C_{13}H_{14}O_2$ requires: C, 77·2; H, 7·0. $C_{13}H_{14}O_2 \cdot H_2O$ requires: C, 71·0; H, 7·3%).

2-Acetyl-2-phenylcyclopentanone (IV). The ethereal solution of the *neutral* product obtained in the foregoing experiment was washed with water, dried and distilled. Thus, 34 g (50%) 2-acetyl-2-phenylcyclopentanone, b.p. 135°/1 mm, was obtained. It gave no colouration with ferric chloride and did not react with 2,4-dinitrophenylhydrazine. $\tilde{\nu}_{max}^{liq}$ 1717 cm^{-1} (broad). (Found: C, 77·3; H, 7·3. $C_{13}H_{14}O_2$ requires: C, 77·2; H, 7·0%).

Reaction of II *with ethyleneglycol.* A mixture of 22 g II, 6·2 g ethyleneglycol and 0·5 g *p*-toluenesulphonic acid in 80 ml dry benzene was distilled azeotropically. The benzene layer was washed with sodium carbonate and water, dried and distilled. Thus, 9 g (30%) of a mixture of the enol ethers VI and VII, b.p. 180–185°/1 mm, was obtained; the product formed a stable monohydrate. $\tilde{\nu}_{max}^{liq}$ 1700, 1723, 3450 cm^{-1}. (Found: C, 67·7; H, 7·6. $C_{15}H_{18}O_3$ requires: C, 73·1; H, 7·3. $C_{15}H_{18}O_3 \cdot H_2O$ requires: C, 68·1; H, 7·6%).

Reaction of II *with ethanol.* A solution of 34 g II, 35 ml ethanol and 0·9 g *p*-toluenesulphonic acid in 190 ml benzene was refluxed azeotropically for 8 hr. After addition of water, the benzene layer was separated, washed with sodium carbonate and water, and dried. Distillation afforded 35 g (quantitative yield) of the enol ethers VIII and IX, b.p. 140°/1 mm, λ_{max}^{EtOH} 250 mμ (3·43). (Found: C, 72·9; H, 8·2; OC_2H_5, 18·6. $C_{15}H_{18}O_3$ requires: C, 78·2; H, 7·8; OC_2H_5, 19·5. $C_{15}H_{18}O_3 \cdot H_2O$ requires: C, 72·7; H, 8·1; OC_2H_5, 18·1%).

Stobbe condensation of the enol ethers (VIII) *and* (IX). A mixture of 12 g (0·5 mole) sodium hydride, 87 g (0·5 mole) diethyl succinate, 82 g (0·33 mole) of the mixture of VIII and IX and 1 ml ethanol in 300 ml dry benzene was refluxed for 16 hr with vigorous agitation. To the cooled mixture, 32 g glacial acetic acid, then ether and water were added. The acidic product was extracted into sodium carbonate solution, acidified with dil. hydrochloric acid and extracted again with ether. Evaporation of the ether yielded 45 g (38%) of an oily acidic product which was used for the next step without further purification. From the neutral ethereal layer, 4·5 g diethyl succinylosuccinate, m.p. 126° (from ethanol), and 40 g (45%) of unchanged enol ethers, b.p. 140°/1 mm, were obtained.

Lactone of 4-hydroxy-1,2-(4'-oxocyclohepteno)-naphthalene-3-acetic acid (X). The oily acidic product from the foregoing experiment (10 g) and 100 g polyphosphoric acid were heated at 100° for 3 hr. After addition of ice-water the mixture was extracted with ether and the extract washed several times with sodium carbonate and water, and dried. Evaporation left an oily residue which crystallized slowly. On trituration with ethanol, it yielded 1·5 g (20%) of X which melted, after recrystallization from butanol, at 193–194°. $\lambda_{max}^{CHCl_3}$ 251 (4·21), 334 mμ (3·68). $\tilde{\nu}_{C=O\,max}^{KBr}$ 1687, 1823 cm^{-1}. (Found: C, 76·6; H, 5·6. $C_{17}H_{14}O_3$ requires: C, 76·7; H, 5·3%). The orange-yellow 2,4-dinitrophenylhydrazone was amorphous.

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SUBSTITUTED 6,7-BENZOCOUMARAN-2-ONES FROM THE STOBBE REACTION OF BENZYL KETONES

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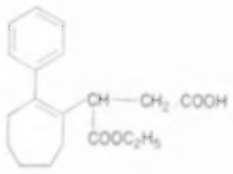
(*Received* 25 *June* 1960)

Abstract—A new type of ring closure, characterized by the formation of a naphthalene nucleus condensed to a γ-lactone ring, is described. It appears to be general for acid-esters, acid-lactones and dicarboxylic acids derived from the Stobbe products of benzyl ketones.

FOR the preparation of tricyclic compounds of type I, starting material II is available by the Stobbe reaction of 2-phenylcycloheptanone (III).

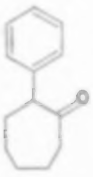
I



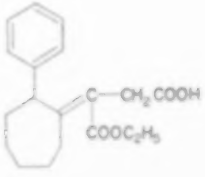
II

This ketone is easily prepared from 2-chlorocycloheptanone and phenylmagnesium bromide.[1,2] Its condensation with diethyl succinate is best carried out with sodium hydride as catalyst in *boiling* benzene. Sodium t-pentoxide gives lower yields and does not permit the recovery of unchanged III, which probably undergoes self-condensation. With sodium hydride, a 30–40 per cent yield of acidic products (expectedly IV) is obtained and 40 per cent of III is recovered.

From the oily acidic products, a solid acid of the expected composition and m.p. 144° was obtained in 7 per cent yield. The spectrum (233 mμ, log 3·89) appears to confirm structure II, as the isomer IV would be expected to absorb at 220–225 mμ.[3] The hypsochromic shift in the spectrum of II as compared with styrene (245 mμ), may be ascribed to steric hindrance,[4] which may also explain the relatively low extinction coefficient.



III

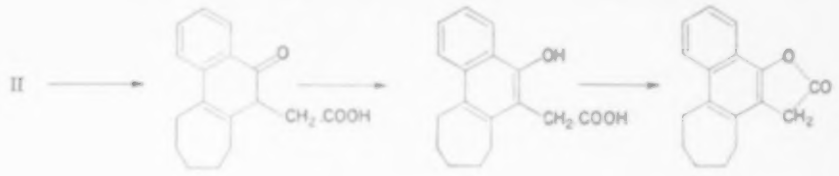


IV

[1] M. S. Newman and M. D. Farbman, *J. Amer. Chem. Soc.* **66**, 1550 (1944).
[2] R. T. Arnold, J. S. Buckley and R. M. Dodson, *J. Amer. Chem. Soc.* **72**, 3153 (1950).
[3] H. E. Ungnade and I. Ortega, *J. Amer. Chem. Soc.* **73**, 1564 (1951).
[4] R. B. Carlin and H. P. Landerl, *J. Amer. Chem. Soc.* **75**, 3969 (1953).

Cyclization of II with polyphosphoric acid gave a neutral product of the formula $C_{17}H_{16}O_2$, which is not a ketone. Its ultra-violet spectrum resembles closely that of naphthalene; in the infra-red, a pronounced maximum was observed at 1823 cm^{-1}, pointing to the presence of a β,γ-unsaturated γ-lactone system[5,6] for which a value of 1800 cm^{-1} is accepted.

The following mechanism for the formation of $C_{17}H_{16}O_2$ is proposed, leading to the structure of 6,7-benzo-4,5-cycloheptenocoumaran-2-one (VII).



V VI VII

Compound II cyclizes to V which isomerizes immediately to the α-naphthol derivative VI in the manner known from the classical α-naphthol synthesis from 3-benzylidenepropionic acid.[7] Compound VI, a derivative of *o*-hydroxyphenylacetic acid, is incapable of independent existence and forms the corresponding coumaran-2-one (VII).[9]

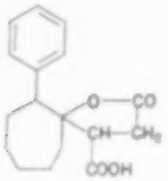
When the crude acidic product of the Stobbe reaction of III is heated with hydrobromic and acetic acids, in order to hydrolyse the ester group in (II) and cause decarboxylation,[10] an oily product is obtained, which upon treatment with polyphosphoric acid again yields VII. The oily product has an infra-red band at 1778 cm^{-1}, and thus appears to be a saturated γ-lactone.[5,6] Formula VIII is in agreement with this and explains the transformation into VII.

The mechanism proposed for the formation of VII suggests that benzyl ketones would undergo in the Stobbe reaction, the same sequence of transformations. Indeed, analogous observations have been made with 2-phenylcyclohexanone and phenylacetone.

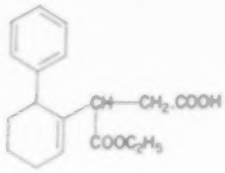
The condensation of 2-phenylcyclohexanone with diethyl succinate in the presence of sodium hydride in boiling benzene give a 61 per cent yield of oily acidic products, but only a 9 per cent yield of a defined acid m.p. 115°, to which according to the spectrum (which is similar to that of benzene) formula IX of 3-carbethoxy-3-(3-phenylcyclohex-1-en-2-yl)-propionic acid is ascribed.[11] Polyphosphoric acid gave X, which has infra-red and ultra-violet spectra (see Table 1) almost identical with VII.

[5] J. F. Grove and H. A. Willis, *J. Chem. Soc.* 877 (1951).
[6] R. S. Rasmussen and R. R. Brattain, *J. Amer. Chem. Soc.* **71**, 1073 (1949).
[7] R. Fittig and H. Erdmann, *Ber. Dtsch Chem. Ges.* **16**, 43 (1883); *Liebigs Ann.* **227**, 242 (1885); R. Fittig, *Ber. Dtsch. Chem. Ges.* **20**, 3182 (1887); R. Fittig and L. Liebmann, *Liebigs Ann.* **255**, 257 (1889); R. Fittig and H. Salomon, *Ibid.* **314**, 73 (1901).
[8] A. v. Baeyer and P. Fritsch, *Ber. Dtsch. Chem. Ges.* **17**, 973 (1884).
[9] In the above scheme, it has been tacitly assumed that in the first step (II → V) the ester group is used directly for cyclization. It is possible that initially ester exchange takes place [C. D. Gutsche and K. L. Seligman, *J. Amer Chem. Soc.* **75**, 2579 (1953); C. D. Gutsche, M. W. Wendt and K. L. Seligman, *Ibid.* **80**, 3711 (1958); W. S. Johnson and A. Goldman, *Ibid.* **67**, 430 (1945)], that the intermediates V and VI contain a carbethoxy, and not a free carboxyl group, and that the molecule of ethyl alcohol is lost in the formation of the coumaran-2-one system (VI → VII).
[10] W. S. Johnson, J. W. Petersen and W. P. Schneider, *J. Amer. Chem. Soc.* **69**, 74 (1947).
[11] C. D. Gutsche and K. L. Seligman, *J. Amer. Chem. Soc.* **75**, 2579 (1953); C. D. Gutsche, M. W. Wendt and K. L. Seligman, *Ibid.* **80**, 3711 (1958).

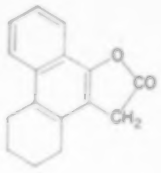
The condensation of phenylacetone with diethyl succinate has been studied by Dice and Allen[12]. The use of sodium hydride in boiling benzene (no reaction takes place in the cold) results in a 80–90 per cent yield of a mixture of two half-esters XI and XII (R = C_2H_5), exhibiting a broad absorption band between 225 and 240 mμ. The mixture of the corresponding acids XI and XII (R = H), obtained by hydrolysis with barium hydroxide, also shows this band. Treatment of the mixture of either



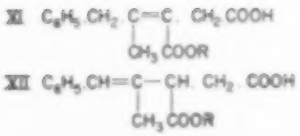
VIII

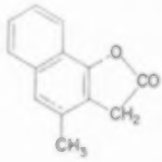


IX



X





XIII

these half-esters or acids with polyphosphoric acid gives the same product, which according to analysis, infra-red absorption at 1823 cm^{-1} and the ultra-violet spectrum (Table 1) is 4-methyl-6,7-benzocoumaran-2-one (XIII).

TABLE 1. SPECTRA OF 6,7-BENZOCOUMARAN-2-ONES, mμ [log ε]; IN CHLOROFORM[13]

Compound				
VII	294 (3·72)	304 (3·70)	318 (3·63)	334 (3·43)
X	291 (3·74)	302 (3·19)	316 (3·62)	331 (3·40)
XIII	284 (3·73)	291 (3·75)	301 (3·43)	327 (3·20)
Naphthalene	267 (3·70)	278 (3·70)	287 (3·60)	311 (3·40)

EXPERIMENTAL

2-Chlorocycloheptanone.[14] A vigorous current of chlorine was bubbled through a suspension of 224 g cycloheptanone in 600 ml water until the weight of the mixture had increased by 140 g (about ½ hr). The heavy layer of 2-chlorocycloheptanone was separated, washed well with water, dried over magnesium sulphate and distilled, yielding 2-chlorocycloheptanone, b.p. 115–116° (30 mm), 175 g (60%).

2-Phenylcycloheptanone. To a solution of phenylmagnesium bromide (1·5 moles; from 36 g magnesium and 235 g bromobenzene in 400 ml dry ether), a solution of 146·5 g (1 mole) 2-chlorocycloheptanone in 300 ml dry ether was added with stirring keeping the mixture boiling gently. Stirring was continued for 1 hr more, the ether distilled off and replaced by 400 ml dry benzene, and

[12] J. R. Dice and G. R. Allen, *J. Amer. Chem. Soc.* **74**, 1231 (1952).
[13] The spectra were examined only above 250 mμ.
[14] M. S. Newman, M. D. Farbman and H. Hipsher, *Organic Syntheses* Coll. Vol. III, p. 188. John Wiley, New York (1955).

the mixture refluxed for 8 hr. After cooling, ice and water were added, and the benzene layer washed with dil. sodium carbonate and water, dried and distilled yielding 2-phenylcycloheptanone (56 g; 30%); b.p. 130–134° (3–4 mm).[15] The 2,4-dinitrophenylhydrazone after recrystallization from ethanol had m.p. 138° (lit.[15] 138°).

3-Carbethoxy-3-(2′-phenylcyclohept-1-en-1-yl)-propionic acid (II)

To a suspension of 12 g (0·5 mole) sodium hydride in 300 ml dry benzene, 87 g (0·5 mole) diethyl succinate, 62 g (0·33 mole) 2-phenylcycloheptanone and 0·5 ml absolute ethanol were added. After refluxing 3 hr with vigorous stirring, the mixture was cooled and acidified with 35 g acetic acid. Ether and water were added and the organic layer extracted several times with 5% sodium carbonate yielding an "acidic fraction". The organic layer was then washed with water, dried and concentrated yielding a "neutral fraction".

Neutral fraction. The residue was triturated with pet ether (40–60°) and yielded 5–6 g diethyl succinosuccinate, from ethanol m.p. 126°. From the filtrate, 24 g (40%) 2-phenylcycloheptanone was recovered.

Acidic fraction. The alkaline extract was acidified with dil. hydrochloric acid and the oily product extracted with ether. The ethereal solution was washed with water and sodium chloride solution, dried and evaporated leaving 31 g (30%) of an oil, which slowly crystallized. Trituration with methanol and two recrystallizations from cyclohexane gave 7 g (7%) of II as colourless crystals, m.p. 143–144°. λ_{max}^{EtOH} 233 mμ (3·89). $\tilde{\nu}_{C=O\,max}^{KBr}$ 1715 cm^{-1}. (Found: C, 72·1; H, 7·2. $C_{19}H_{24}O_4$ requires: C, 72·1; H, 7·6%).

6,7-*Benzo-4,5-cycloheptenocoumaran-2-one* (VII)

(a) A mixture of 2 g II and 50 g polyphosphoric acid was heated with stirring at 100° for 3 hr. After the addition of ice and water, the product recrystallized from butanol yielding 1·3 g (82%) of VII, m.p. 168°. $\lambda_{max}^{CHCl_3}$ 294 (3·72), 304 (3·70), 318 (3·63), 334 mμ (3·43). $\tilde{\nu}_{C=O\,max}^{KBr}$ 1823 cm^{-1}. (Found:C, 80·5; H, 6·7. $C_{17}H_{16}O_2$ requires: C, 80·9; H, 6·3%).

(b) The same product is obtained in better yield as follows: The acidic fraction (5 g), 50 ml hydrobromic acid (48%), 75 ml acetic acid and 25 ml water were refluxed for 14 hr. The volatile products were removed *in vacuo* and the residue treated with water and a mixture of ether and ethyl acetate (1 : 1). Removal of the organic solvents left an oily residue which after distillation yielded 2·5g (53%) of an oil, perhaps VIII, exhibiting two strong carbonyl bands in the infra-red at 1717 and 1778 cm^{-1}.

The distillate (2 g) was heated with 50 ml polyphosphoric acid at 100° for 3 hr. The product after addition of ice and water, was recrystallized from butanol yielding 1·2 g (70%) of VII, m.p. and mixed m.p. 168°.

4-*Methyl*-6,7-*benzocoumaran-2-one* (XIII)

(a) A mixture of 67 g (0·5 mole) phenylacetone, 130 g (0·75 mole) diethyl succinate and 1 ml absolute ethanol was added to a suspension of 18 g (0·75 mole) sodium hydride in 300 ml dry benzene and the mixture refluxed for 6 hr. After cooling, 50 ml glacial acetic acid, ether and water were added. The acidic product was extracted from the benzene layer with sodium carbonate (5%), acidified with dil. hydrochloric acid and again ether extracted. The product (110 g; 84%) distilled at 200–210° (0·5 mm). The ultra-violet absorption [in ethanol broad band from 225 mμ (log ε 4·16) to 240 mμ (log ε 4·15)] indicated the presence of a mixture of 3-carbethoxy-4-methyl-5-phenyl-3- and -4-pentenoic acid (XI, XII; R = C_2H_5). This mixture (10 g) treated with 150 g polyphosphoric acid, yielded 5·7 g (75%) of XIII which recrystallized from butanol, m.p. 158°. $\lambda_{max}^{CHCl_3}$ 284 (3·73), 291 (3·75), 301 (3·43), 327 mμ (3·20). $\tilde{\nu}_{C=O\,max}^{KBr}$ 1823 cm^{-1}. (Found: C, 78·9; H, 5·4. $C_{12}H_{10}O_2$ requires: C, 78·8; H, 5·1%).

(b) Isolation of the dicarboxylic acids XI and XII (R = H). To a solution of 400 g barium hydroxide in 1 l. 50% ethanol, 20 g of the half-esters XI and XII (R = C_2H_5) was added and the mixture boiled for 5 hr. After cooling, the barium salts were collected and acidified with dil. hydrochloric acid. The free organic acids separated as a white solid, which after two recrystallizations from toluene had m.p. 148–152° and, according to Dice and Allen[12], was a mixture of the two dicarboxylic

[15] C. D. Gutsche, *J. Amer. Chem. Soc.* **71**, 3513 (1949).

acids. The ultra-violet spectrum showed a broad band from 210 mμ (log ε 4·07) to 242 mμ (log ε 3·84), indicating the presence of such a mixture. (Found: C, 66·8; H, 6·3. $C_{18}H_{14}O_4$ requires: C, 66·7; H, 6·0%).

Cyclization of 2 g of this product with 50 g polyphosphoric acid yielded 1·2 g (82%) of XIII, m.p. and mixed m.p. 158°. $\lambda_{max}^{CHCl_3}$ 283 (3·77), 291 (3·77), 301 (3·56), 327 mμ (3·34). $\tilde{\nu}_{CO\,max}^{KBr}$ 1823 cm^{-1}.

3-Carbethoxy-3-(3′-phenylcyclohexen-1-en-2-yl)-propionic acid (IX)

To a suspension of 4·2 g (0·175 mole) sodium hydride in 100 ml dry benzene, 30·5 g (0·175 mole) diethyl succinate, 20 g (0·115 mole) 2-phenylcyclohexanone[11] and 0·3 ml absolute ethanol were added, and the mixture boiled for 6 hr. After cooling, 12 ml glacial acetic acid, ether and water were added. The organic layer was extracted several times with sodium carbonate and the alkaline extract acidified with dil. hydrochloric acid. The oily material, which separated, was extracted with ether and the ether dried and evaporated leaving an oily residue (21 g; 61%). Upon trituration with a mixture of benzene and methanol it yielded 3 g (9%) of IX as colourless crystals, m.p. 115° after recrystallization from cyclohexane. λ_{max}^{EtOH} 242 (2·45), 247 (2·42), 254 (2·43), 259·1 mμ (2·45). (Found: C, 71·0; H, 7·4. $C_{18}H_{22}O_4$ requires: C, 71·5; H, 7·3%).

6,7-Benzo-4,5-cyclohexenocoumaran-2-one (X)

Cyclization of 2 g IX with 60 g polyphosphoric acid yielded 1·9 g (80%) X, from butanol m.p. 182°. $\lambda_{max}^{CHCl_3}$ 291 (3·73), 302 (3·79), 316 (3·62), 331 mμ (3·40). $\tilde{\nu}_{C=O\,max}^{KBr}$ 1823 cm^{-1}. (Found: C, 80·4; H, 5·8. $C_{16}H_{14}O_2$ requires: C, 80·7; H, 5·9%).

Tetrahedron, 1960, Vol. 11, pp. 163 to 170. Pergamon Press Ltd. Printed in Northern Ireland

EQUILIBRIUM RELATIONSHIP OF D-HOMO KETOLIC SYSTEMS[1]

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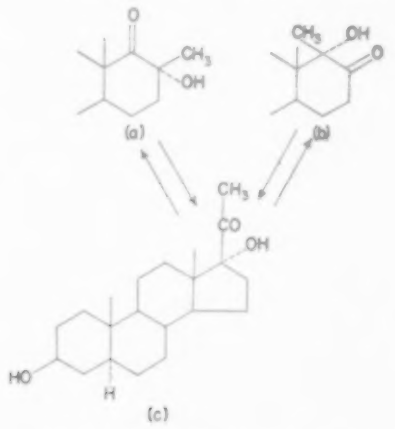
Abstract—The ability of the various D-homo ketolic isomers arising from 17-hydroxy-20-keto steroids to equilibrate with each other under alkaline as well as Lewis acid conditions has been demonstrated and discussed.

THE D-homoannulation rearrangement of 17-hydroxy-20-keto steroids had, until very recently, been considered to pursue a relatively well-defined reaction course as predetermined in large measure by reagent control. In the latter regard either alkali, heat or Lewis acids had been generally employed to evoke this change. These transformations and their mechanistic significance, in fact, have been discussed at some length just recently.[1c] In 1958 Elphimoff-Felkin and Skrobek published a paper[2] in which they reported the important observation that the isomeric ketolic systems A and B, derived from Reichstein's substance L (C), could be interconverted by aluminum t-butoxide or boron trifluoride. The conclusion was made, moreover, that this interconversion arose by retrogression to the normal steroid C.



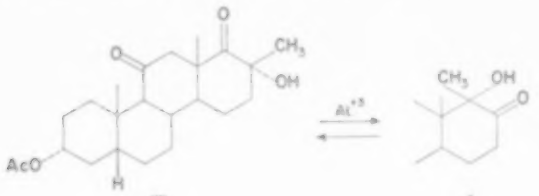
These findings were the first indication of the complexity and lack of unidirectional character of this ring expansion reaction.

Independent of Elphimoff-Felkin and Skrobek, we had made the same

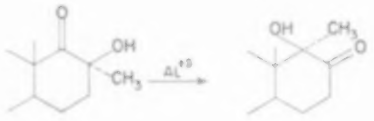
[1] For preliminary accounts of this work see [a] D. Taub and N. L. Wendler, *Chem. & Ind.* 902 (1959); [b] N. L. Wendler, D. Taub and R. W. Walker, *Ibid.* 903 (1959); [c] N. L. Wendler, D. Taub and R. Firestone, *Experientia* XV, 237 (1959).

[2] I. Elphimoff-Felkin and A. Skrobek, *C.R. Acad. Sci., Paris* **246**, 2497 (1958). For details, *Idem, Bull. Soc. Chim.* 742 (1959). Through inadvertence on our part we had overlooked in our earlier communications, the contributions of Madame I. Elphimoff-Felkin to the general knowledge of the D-homo rearrangement. See also ref. 4; and W. Klyne and C. W. Shoppee, *Chem. & Ind.* 470 (1952).

observation.[1c] We found that 3α-acetoxy-17α-hydroxy-17β-methyl-D-homo-5β-androstane-11,17a-dione (III)[3] and 3α-acetoxy-17aα-hydroxy-17aβ-methyl-D-homo-5β-androstane-11,17-dione (I)[3] could be interconverted by refluxing either pure isomer with aluminum t-butoxide in toluene for 20 hours; there was produced, thereby, an equilibrium mixture consisting of approximately 65 per cent III and 35 per cent I. We further examined the remaining D-homo isomers and found that the 17aβ-hydroxy ketol (II)[3] remains unchanged under the equilibrating conditions with aluminum t-butoxide whereas the 17β-hydroxy ketol (IV)[3] is converted completely to II; there was no evidence of an equilibrium relationship between II and IV.



III I



IV II

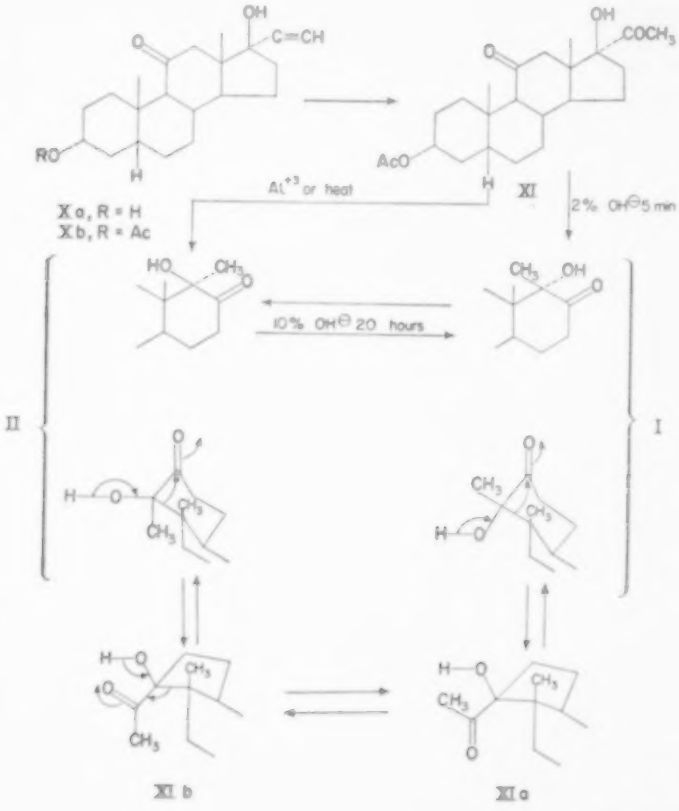
In the light of the fact that tracer studies have precluded the possibility of methyl migration in the formation of these D-homo systems,[4] the fact of their interconvertibility emphasizes their capacity to exist in a reversible relationship with a 17-hydroxy-20-keto steroid precursor.

Several years ago Madame Elphimoff-Felkin[5] had considered the role of conformational control of bond migration in the D-homo rearrangement with Lewis-acids. More recently we discussed this same concept and extended it to the alkaline catalyzed ring expansion reaction.[1c] Several considerations have been introduced into this general area however, which make the conformational argument less definitive than originally anticipated. Recent findings, for example, suggest the possibility at least that the 17α-ketol (III) may have its D-ring in the boat conformation.[6] Further, the conformational argument is unable to accommodate identical bond movement in the nitrous acid-amine rearrangement of C17-epimeric 17-hydroxy 20-amino pregnane derivatives.[7]

In studies on the alkaline catalyzed D-homo rearrangement we found that kinetic as well as equilibrium products are to be expected.[1b] Earlier studies had demonstrated, for example, that D-homoannulation of 17β-hydroxy-20-keto-17-isopregnane

[3] N. L. Wendler and D. Taub, *Chem & Ind.* 505 (1955); N. L. Wendler, D. Taub, S. Dobriner and D. Fukushima, *J. Amer. Chem. Soc.* **78**, 5027 (1956).
[4] R. B. Turner, M. Perelman and K. T. Park, Jr., *J. Amer. Chem. Soc.* **79**, 1108 (1957).
[5] I. Elphimoff-Felkin, *Bull. Soc. Chim.* 1845 (1956).
[6] [a] N. L. Wendler, *Chem. & Ind.* 1652 (1958); *J. Amer. Chem. Soc.* In press; [b] R. Rosenfeld, *Ibid.* **77**, 6585 (1957).
[7] [a] N. L. Wendler, D. Taub and H. L. Slates, *J. Amer. Chem. Soc.* **77**, 3559 (1955); [b] F. Ramirez and S. Stafiej, *Ibid.* **77**, 134 (1955); **78**, 644 (1956).

derivatives is catalyzed by Lewis acids to give 17aβ-ketols (type II) and by alkali to yield 17aα-ketols (type I) as the major, if not exclusive, product.[8] We had prepared 3α-acetoxy-17β-hydroxy-17-isopregnane-11,20-dione (XI) by Stavely[9] hydration of the ethinyl carbinol (Xb).[10] The 17-isopregnanolone was found to be quite unstable, melting at 120–130° with phase change and total rearrangement, to the 17aβ-ketol (II), m.p. 223–226°. Similarly, compound XI was converted to the 17aβ-ketol (II) essentially quantitatively an alumina. On the other hand, treatment of the 17-isopregnanolone (XI) with boiling 2 per cent methanolic potassium hydroxide for 5 minutes produced the known 17aα-ketol (I) in essentially quantitative yield. The latter represents the kinetic product of rearrangement since both the 17-isopregnanolone (XI) as well as the 17aα-ketol (I), when boiled for 20 hours with methanolic potassium hydroxide, yield the same 50 : 50 $\pm$ 10 per cent equilibrium mixture of 17aα-ketol (I) and 17aβ-ketol (II). Likewise, treatment of the 17aβ-ketol (II) also produced the same equilibrium product I $\leftrightharpoons$ II.



[8] [a] C. W. Shoppee and D. A. Prins, *Helv. Chim. Acta* **26**, 185, 201, 1004 (1943); [b] R. B. Turner, *J. Amer. Chem. Soc.* **75**, 3484 (1953). R. B. Turner, R. Anliker, R. Helbling, J. Meier and H. Heusser, *Helv. Chim. Acta* **35**, 411 (1955).

[9] H. E. Stavely, *J. Amer. Chem. Soc.* **62**, 489 (1940); see also ref. 8*b*.

[10] [a] L. H. Sarett, *J. Biol. Chem.* **162**, 601 (1946); [b] N. L. Wendler, R. P. Graber and G. G. Hazen, *Tetrahedron* **3**, 144 (1958).

Again the formation of an equilibrium product requires that the pertinent D-homo isomers be capable of existing in a reversible relationship with a 17-hydroxy-20-keto pregnane; only through mediation of the latter can a configurational inversion reasonably occur at C-17a. Further, assuming that these D-homo systems possess chair conformations and rearrange from same, it follows that the equilibration of the 17aα-ketol (I) and 17aβ-ketol (II) would take place by way of starting 17-isopregnanolone (XI) and not its C-17α-OH isomer (XII). The formation of the 17aα-ketol (I) as the kinetic product is in accord with the postulates expressed by Turner[8b] wherein the probable *trans* OH *vs* C=O alignment in the transitional species (compare XIa) predicts the formation of I.

The alkaline D-homoannulation of 17α-hydroxy-20-ketopregnanes (XII) has by past experience[6,3] resulted in the predominant formation of the 17aβ-ketol (II), with the 17aα-ketol (I) being formed as a minor product. The product expected by conformational considerations, on the other hand, is the 17β-ketol (IV). The fact that until very recently[11] this isomer had never beeen identified from a D-homo rearrangement reaction was in itself mysterious. The present authors construed this to indicate the possible instability of this isomer, IV, under the alkaline rearrangement conditions in analogy with the behavior of I[1c]. In fact it was later demonstrated that this isomer, IV, is indeed unstable to the 20 hour equilibration conditions with alkali and does give I and II in the same essential ratio as that previously observed to be produced from the latter isomers themselves. The suggestion was therefore made that IV, like I, is the kinetic product of rearrangement. This conclusion is now known

[11] Dr. Fukushima of the Sloan Kettering Institute for Cancer Research has informed us recently that he has synthesized 3β,17β-dihydroxy-17α-methyl-D-homoandrostane-17a-one (see method, ref. 3) and found this compound to be identical with an unknown product isolated in about 7% yield from the reaction of base with Reichstein's Substance L. [See also *J. Amer. Chem. Soc.* **77**, 6585 (1955).]

not to be true. Under conditions less than those necessary to produce equilibrium, the isomer, IV, is recovered largely unchanged whereas the parent steroid (XII) is converted to II (major) and I (minor). Only under the more prolonged conditions of alkaline treatment is IV, in turn, converted to the equilibrium product. Consequently, since IV is finally ruled out as the kinetic product of rearrangement of XII, the conformational argument in whose support it was originally employed is correspondingly invalidated. The kinetic product of rearrangement of XII appears to be the 17aβ-ketol (II). This is suggested by the observation that when XII is refluxed for 4 hours with 5 per cent methanolic potassium hydroxide the product by infrared analysis consisted of 68 per cent 17aβ-ketol (II) and 32 per cent 17aβ-ketol (I). On the other hand, under the 20 hour conditions of alkaline equilibration, a product ratio of 50 : 50 $\pm$ 10 per cent was realized.

In contrast to the other D-homo isomers, the 17α-hydroxy ketol (III) is in large measure unaffected by the conditions of base equilibration although traces of the ketols I and II are nonetheless indicated by paper partition chromatography and infrared spectroscopy. Prolonged treatment (4–5 days) with alkali, however, failed to increase the amount of I and II, but resulted, on the other hand, in considerable decomposition of an undetermined character.

The methods employed for analyzing the products obtained from the equilibration experiments described were threefold: Paper partition chromatography on Whatman No. 1 or 4 paper utilizing benzene–cyclohexane 1 : 3 as the mobile phase and formamide as the stationary phase, effected good resolution of the 17aα and 17aβ-ketols, both of which give positive Zimmermann color reactions.[12] The 17α and 17β-hydroxy ketols, which were also easily separated, do not give a positive Zimmermann reaction but can be detected by the iodine vapor technique.[13]

Analysis of the isomeric mixtures was carried out by means of infrared spectrophotometry. The working curve method was used, in which a series of known mixtures of the various isomers was made up, the infrared curves of which were compared directly with the unknowns. This procedure, besides establishing the percent isomer ratio within the desired limits ($\pm$5 per cent), also afforded a direct comparison of the entire spectrum in the 2–15 micron region and thus served as a control in establishing the absence of impurities or other isomers which might invalidate the results.

The experimental work was carried out on a Baird double beam infrared spectrophotometer with NaCl optics (Model B), using a cell of 0·10 mm path length and at a fixed concentration of 10 mg solute/78 mg chloroform. Listed below are the most characteristic absorption bands of the four isomers. In most instances, only two isomers were present in any given unknown. With the few cases where more than two isomers were present, it was sometimes necessary to utilize both characteristic bands listed.

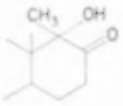
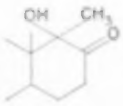
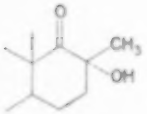
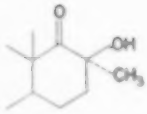
Finally, in many of the cases, direct isolation of the components of the isomeric product was carried out either by alumina chromatography, which was less satisfactory, or by chromatography on Whatman No. 3 paper. In the instances where the 17β-hydroxy ketol and 17aβ-ketol preponderated direct crystallization sufficed to separate these compounds.

[12] Procedure of K. Savard, *J. Biol. Chem.* **202**, 457 (1953).
[13] G. B. Marini-Bettolo-Marconi and S. Guarino, *Experientia* **6**, 309 (1950).

In conclusion it may be said that the D-homoannulation rearrangement has revealed itself to be much more diverse in character than previously appreciated. It is a transformational type subject to all manner of directional control giving as it does kinetic products, products of reagent control and equilibrium products. The lack of parallelism in the behavior to alkali of the 17 ketones *vis-a-vis* the 17a ketones is mystifying as is the unique stability, for example, of the isomer III. Consequently, at the present time, no single concept seems adequate to embrace logically and consistently all facets of this transformation.

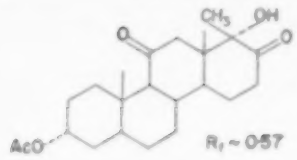
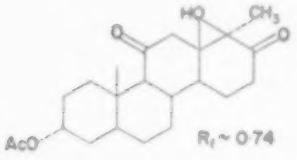
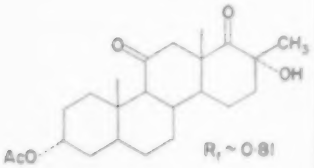
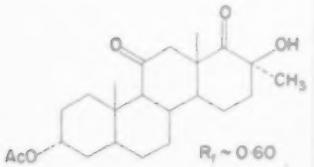
EXPERIMENTAL

3α-Acetoxy-17β-hydroxy-17-isopregnane-11,20-dione (XI). Acetylation of 4·9 g of the 3α-hydroxy-ethinyl carbinol (Xa)[13] gave the corresponding 3α-acetate (Xb), 4·88 g, m.p. 184–186°. A mixture of 4·78 g Xb, 9·0 g mercuric chloride and 1·5 cc freshly distilled aniline in 200 cc benzene and 50 cc water was stirred at 60° for 20 hr. The mixture was cooled, filtered, washed with water, dil hydrochloric acid, dil potassium bicarbonate solution, saturated sodium chloride solution and dried over magnesium sulfate. The yellow residue which showed no tendency to crystallize was partitioned as follows:[14]

Isomer	Major characteristic absorption bands	For detection in isomer
 I	10·35 μ	IV
	10·85 μ	II, III
 II	10·69 μ	I, III, IV
 III	9·40 μ	IV
	9·98 μ	I, II
 IV	9·95 μ	I
	10·82 μ	II, III

[14] Procedure of R. F. Hirschmann of these laboratories.

It was dissolved in 150 cc formamide and extracted successively with hexane, cyclohexane, cyclohexane–benzene 1 : 4, cyclohexane–benzene 1 : 1, benzene and benzene–chloroform 1 : 2. Each extract was washed with water, dried over sodium sulfate and concentrated to dryness. The benzene–cyclohexane 1 : 1 and benzene extracts crystallized from 50% ether–pet ether to give 2·01 g of the 17-isopregnane (XI) which melted nearly completely at 120–135°, resolidified and finally melted at 223–226°. This behavior indicated thermal D-homoannulation to the 17aβ-hydroxy ketol (II) (see below). XI had $[\alpha]_D^{Chf.}$ +46°,[15] $\lambda_{max.}^{Chf.}$: 2·74, 2·85–2·90, 5·78, 5·86, 8·0 μ. (Found: C, 70·94; H, 8·64. Calc. for $C_{23}H_{34}O_3$: C, 70·74; H, 8·71%).

Isomer equilibrated	Reagent	Product composition	Component isolated
 I	Al^{+3} $OH^{\ominus}$	65% III; 35% I 55% I; 45% II	III—Al_2O_3—chromatography II—Chromatography & crystallization
 II	Al^{+3} $OH^{\ominus}$	~100% II 50% I; 50% II	II—direct crystallization I—Paper chromatography
 III	Al^{+3} $OH^{\ominus}$	60% III; 40% I 70% III; 20% I ~10% II	III—Al_2O_3—chromatography III—Al_2O_3—chromatography
 IV	Al^{+3} $OH^{\ominus}$	95% II 60% I; 40% II	II—Crystallization I and II—Paper Chromatography

The hexane and cyclohexane fractions consisted primarily of a U.V. absorbing, non-crystalline yellow material which gave an instantaneous strong Zimmermann test and which was very mobile on paper. By analogy with Turner's[6b] this material could be a 17a-methyl, 17a-anilino-17-keto-D-homo-5β-androstane.

That ring D in XI is 5-membered was demonstrated by successive treatment of XI with lithium

[15] The ΔM_D XII–XI is +148°. This compares with values of +135°, +91° and +191° (in various solvents) for three pairs of normal and iso-17-hydroxy-20-ketopregnanes. Data from Pouvoir Rotatoire Naturel I, J. P. Mathieu and A. Petit, *Stéroides*. Masson et Cie., Paris (1956).

aluminum hydride in refluxing tetrahydrofuran and sodium periodate in aqueous methanol to give in excellent yield 3α,11β-*dihydroxy*-5β-*androstane*-17-*one*, m.p. 231–234°, identical with an authentic specimen.[16]

Rearrangement of 3α-*acetoxy*-17β-*hydroxy*-17-*isopregnane*-11,20-*dione* (XI)

(a) *Treatment with* 2% *alkali.* A solution of 100 mg XI in 5 cc methanol was brought to boiling and treated with 1 cc of a solution containing 1 g potassium hydroxide in 10 cc water. The reaction mixture was allowed to reflux for 5 min, then chilled and acidified with dil aqueous hydrochloric acid. The quenched reaction mixture was evaporated *in vacuo* and the residue extracted with ethyl acetate. The ethyl acetate extract was washed neutral with bicarbonate, the solvent evaporated, and the residue acetylated in 0·5 cc pyridine with 0·5 cc acetic anhydride. The product from the acetylation crystallized spontaneously from ether to give 3α-*acetoxy*-17aα-*hydroxy*-17aβ-*methyl* D-*homo*-5β-*androstane*-11,17-*dione* (I), m.p. 179–181°; mixed m.p. with authentic I not depressed. The infrared spectra of the two samples were identical. A sample of the total product before crystallization analysed in the infrared for 95% 17aα-hydroxy ketol (I).

(b) *Prolonged treatment with* 10% *alkali.* A solution of 100 mg XI in 10 cc methanol was treated with 1 g potassium hydroxide in 1 cc water and the reaction mixture refluxed for 20 hr in a nitrogen atmosphere. The product was acetylated and analyzed in the infrared for 55% 17aβ-hydroxy ketol (II) and 45% 17aα-hydroxy ketol (I). Chromatography followed by crystallization afforded crystalline II, m.p. 220–225°; mixed m.p. with authentic II not depressed. The infrared spectra of the two samples were identical.

(c) *Alumina.* A 100 mg sample of XI dissolved in 10 cc benzene was slurried for 24 hr with 2·5 g neutral alumina. The total product analyzed in the infrared for at least 95% 17aβ-hydroxy ketol (II). The total product recrystallized from acetone–ether melted at 223–227°.

(d) *Rearrangement by heat.* A sample of XI was warmed in a capillary tube. It partly melted near 120°, resolidified and completely melted at 223°. Paper chromatography of the melt in the benzene–cyclohexane 1 : 3–formamide system showed the presence only of the 17aβ-hydroxy ketol (II). On remelting, the sample had m.p. 223–226°; mixed m.p. with authentic II, 222–225°.

Equilibration experiments with the isomeric D-*homo ketols. General procedures*

(a) *Aluminum t-butoxide catalyzed equilibrations* were conducted by refluxing a solution of e.g. 500 mg of the pertinent ketol in 10 cc toluene with 500 mg aluminum t-butoxide in a nitrogen atmosphere for 20–24 hr. At the conclusion of this period of reflux, the reaction mixture was cooled, acidified and the toluene evaporated *in vacuo*. The residue was dissolved in ether and the ether extract washed with bicarbonate, dried and evaporated to dryness. The residue was in each instance analyzed for percent composition by infrared spectroscopy, submitted to paper partition chromatography and the components isolated in specific instances.

(b) *Alkali catalyzed equilibrations* were conducted by refluxing a solution of e.g. 500 mg of the pertinent ketol in 10 cc methanol containing 1 g potassium hydroxide and 1 cc water for 20–24 hr in a nitrogen atmosphere. At the conclusion of this period, the methanol was removed *in vacuo* and the product extracted with ethyl acetate. The ethyl acetate extract was evaporated and the residue acetylated with acetic anhydride in pyridine. The total product was subsequently submitted to paper partition chromatography and analyzed by infrared spectroscopy for component composition. In specific instances the isomers were isolated.

[16] N. L. Wendler, D. Taub and R. P. Graber, *Tetrahedron* 7, 173 (1959).

Tetrahedron, 1960, Vol. 11, pp. 171 to 182. Pergamon Press Ltd. Printed in Northern Ireland

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SMALL-RING COMPOUNDS—XXIX

A REINVESTIGATION OF THE SOLVOLYSIS OF CYCLOPROPYLCARBINYL CHLORIDE IN AQUEOUS ETHANOL. ISOMERIZATION OF CYCLOPROPYLCARBINOL*†

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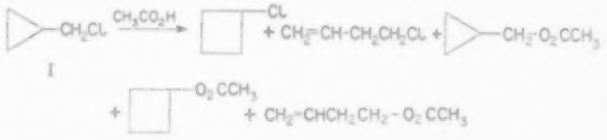
Abstract—The solvolysis of cyclopropylcarbinyl chloride in 80% ethanol is attended by substantial rearrangement—not only do the solvolysis products include cyclobutyl and allylcarbinyl alcohols and ethyl ethers but cyclopropylcarbinyl chloride undergoes partial rearrangement by "internal return" to cyclobutyl and allylcarbinyl chlorides. Nuclear magnetic resonance spectroscopy has been used to demonstrate that considerable isotope-position rearrangement takes place under quite mild conditions in the reactions of deuterium-labeled cyclopropylcarbinol and cyclobutanol with thionyl chloride. Isotope-position changes have been studied in the acid-induced isomerization of cyclopropylcarbinol.

INTRODUCTION

STUDIES of the solvolysis of cyclopropylcarbinyl chloride (I) in aqueous ethanol by two groups of workers have given somewhat different results. Chloride (I) was first obtained pure§ by Mazur[1] via vapor-phase photochlorination of methylcyclopropane, and he made a rather extensive investigation of its solvolysis reactions. The behavior of I in acetic acid was most unusual when viewed in the light of the knowledge of the time. In the first place, chloride I in this and other solvents was most uncommonly reactive for a saturated primary chloride; and, second, by the time 30 per cent of the theoretical amount of chloride ion was liberated, I essentially was completely converted to a mixture of substantially less reactive cyclobutyl and allylcarbinyl chlorides in a ratio of about 1·7 to 1. The acetolysis products arising from I were cyclopropylcarbinyl and cyclobutyl acetates in the ratio of about 2·6:1 with perhaps a few percent of allylcarbinyl acetate as well.



Similar, but much less extreme, behavior was noted in 50 per cent aqueous ethanol. In this solvent, rearrangement was found to occur at only about one-third the rate of

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‡ Arthur Amos Noyes Research Fellow.

§ As judged by the absence of infrared absorption corresponding to cyclobutyl and allylcarbinyl chlorides.

[1] J. D. Roberts and R. H. Mazur, *J. Amer. Chem. Soc.* **73**, 2509 (1951).

liberation of chloride ion. Although the reaction products were not determined in 50 per cent ethanol, the neutral heterogeneous reaction with water was found to give rearranged chlorides and a mixture of cyclopropylcarbinol cyclobutanol, and allylcarbinol in about the same proportions as formed from the treatment of either cyclopropylcarbinylamine or cyclobutylamine with nitrous acid.

The rearrangement of chloride I to cyclobutyl and allylcarbinyl chlorides in solvolytic reactions is now well understood as an example of "internal return" from an "intimate" carbocation-chloride ion pair, which phenomenon was first clearly demonstrated by Young, Winstein and Goering[2] for α,α-dimethylallyl chloride and subsequently scrutinized with great care by Winstein *et al.*[3] The abnormally high solvolytic reactivity of I and its tendency both to rearrange to isomeric chlorides and to form rearranged solvolysis products speak strongly for the intermediacy of a bridged, rather substantially stabilized carbonium ion embodying structural elements of the cyclopropylcarbinyl, cyclobutyl, and allylcarbinyl cations—the "non-classica" bicyclobutonium cation (II).[4]

II

Chloride I has also been prepared by Brown and Borkowski[5] by liquid-phase chlorination of methylcyclopropane. The carefully purified product was judged to be 94 mole per cent I by analysis of its cooling curve. Solvolysis rate studies in 80 per cent ethanol showed the reactivity to be about 1/15 as large as t-butyl chloride, whereas a normal saturated primary chloride might be expected to form carbonium ions about 10^{-10} times slower than t-butyl chloride.[6] No evidence for internal-return isomerization of chloride I can be deduced from the reported solvolysis rate measurements,[5] which were stated to be in accord with simple, first-order kinetics throughout. The solvolysis products were not investigated.

While the discrepancies between the above investigations may seem trivial, the finding of simple, first-order kinetics for the solvolysis of I[5] in aqueous ethanol, buttressed by the reported[7] formation of substantially pure cyclopropylcarbinyl ethyl ether from the solvolysis of cyclopropylcarbinyl benzenesulfonate in absolute ethanol,* has been taken as evidence for the conclusion that cyclopropylcarbinyl

* The significance of the particular experiment as a *solvolysis* is open to question. To be sure, Bergstrom and Siegel report an apparently insignificant increase in the first-order solvolysis rate constant of the benzenesulfonate in the presence of sodium ethoxide (from $6{\cdot}3 \times 10^{-5}$ to $7{\cdot}2 \times 10^{-5}$ sec^{-1} with 0·0266 M ethoxide) so that one might well infer a negligible contribution of non-rearranging S_N2 type substitution between the ester and ethoxide ion. However, a simple calculation shows that [benzenesulfonate] . [ethoxide] was $2{\cdot}1 \times 10^3$ *times greater* under the conditions where the reaction products were determined than under the conditions used for the kinetic runs. It should be clear that the seemingly small increase in the ethanolysis rate constant with a small amount of added ethoxide might well mean essentially exclusive S_N2 reaction where the arithmetic product of ester and ethoxide concentrations is so very high.

[2] W. G. Young, S. Winstein and H. L. Goering, *J. Amer. Chem. Soc.* **73,** 1958 (1951).
[3] S. Winstein and A. H. Fainberg, *J. Amer. Chem. Soc.* **80,** 459 (1958) and earlier papers.
[4] R. H. Mazur, W. N. White, D. A. Semenow, C. C. Lee, M. S. Silver and J. D. Roberts, *J. Amer. Chem. Soc.* **81,** 4390 (1959).
[5] H. C. Brown and M. Borkowski, *J. Amer. Chem. Soc.* **74,** 1894 (1952).
[6] L. C. Bateman, K. A. Cooper, E. D. Hughes and C. K. Ingold, *J. Chem. Soc.* 925 (1940); E. Grunwald and S. Winstein, *J. Amer. Chem. Soc.* **70,** 841 (1948); S. Winstein, E. Grunwald and H. W. Jones, *Ibid.* **73,** 2700 (1951).
[7] C. G. Bergstrom and S. Siegel, *J. Amer. Chem. Soc.* **74,** 145 (1952).

derivatives may solvolyze by way of a cationic intermediate without formation of rearrangement products and that the enhanced rate of solvolysis may not be due to any driving force for formation of a non-classical cation.[8] It has been further maintained that the extraordinary facile interconversions of cyclopropylcarbinyl, cyclobutyl, and allylcarbinyl derivatives observed in amine-nitrous acid and many other carbonium ion type reactions[1,4] need not be typical of solvolysis or other reactions occurring under very mild conditions. The results obtained in the solvolysis of chloride I by Mazur[1] have been attributed to impurities[8] on the grounds that material of 94 per cent purity, prepared by Brown and Borkowski[5] gave a first-order rate of hydrogen chloride production.

The above criticisms of Mazur's work are important since they clearly strike at the very heart of the argument[4] for intervention of non-classical ions such as II in carbonium ion-type interconversion reactions of cyclopropylcarbinyl, cyclobutyl, and allylcarbinyl derivatives. Although, as indicated, the factual basis for the criticisms leaves much to be desired, the importance of the points in question has prompted us to repeat and extend much of the earlier work. The investigation has been greatly facilitated by the use of vapor-phase chromatography (v-p-c) which technique was not available at the time of the previous investigation. Fortunately, samples of I prepared by Mazur in 1950 were still available for analysis.

EXPERIMENTAL RESULTS

Vapor-phase chromatography is well suited for the analysis of cyclopropylcarbinyl cyclobutyl, and allylcarbinyl chlorides. Fig. 1A shows a chromatogram* for a typical chloride mixture resulting from the reaction of cyclopropylcarbinol with thionyl chloride. The composition of the mixture (69 per cent cyclopropylcarbinyl chloride, 27 per cent cyclobutyl chloride and 4 per cent allylcarbinyl chloride) agrees well with Mazur's infrared analysis of a mixture prepared in the same way (67 per cent cyclopropylcarbinyl chloride, 30 per cent cyclobutyl chloride, and 3 per cent allylcarbinyl chloride). The sample of chloride I used in Mazur's kinetic measurements[1] was found to be 99+ per cent cyclopropylcarbinyl chloride. Only a faint indication of allycarbinyl chloride was noted in the v-p-c analysis. Consequently, there seems to be no question that the internal-return mechanism must be invoked to account for the isomerization of the chloride during the solvolysis reaction because the chloride does not rearrange at the solvolysis temperature in the absence of an ionizing solvent or ionizing agent such as zinc chloride.

The internal consistency and clarity of the data reported by Mazur[1] for chloride I in acetic acid leave no room for doubt that, in acetic acid, solvolysis and rearrangement are very intimately related. The results in all respects are consistent with the formation of II (or its intimate ion-pair with chloride ion). We have seen no need to repeat this work nor the measurements of the kinetics of the solvolysis of I in 50 per cent aqueous ethanol since the essential point in question as to whether internal-return isomerization actually occurred has been answered in the affirmative by the finding that the starting chloride was even purer than advertised and by verification of the validity of the

* All vapor-phase chromatographic analyses reported herein were obtained with Perkin–Elmer Vapor Fractometer using "A"-type packing (diisodecyl phthalate on crushed firebrick).

[8] H. C. Brown, *Falk-Plaut Lecture*, Columbia University, March 6 (1957) and seminar at Harvard University, October 10 (1958).

infrared analysis used to establish the presence of rearranged chloride in the unreacted halide isolated from the reaction mixture.

We turn next to consideration of the solvolysis of I in 80 per cent ethanol for which clean, first-order kinetics are reported[5] and for which it has been inferred that no rearrangement products are formed.[8] The following technique was used in studying

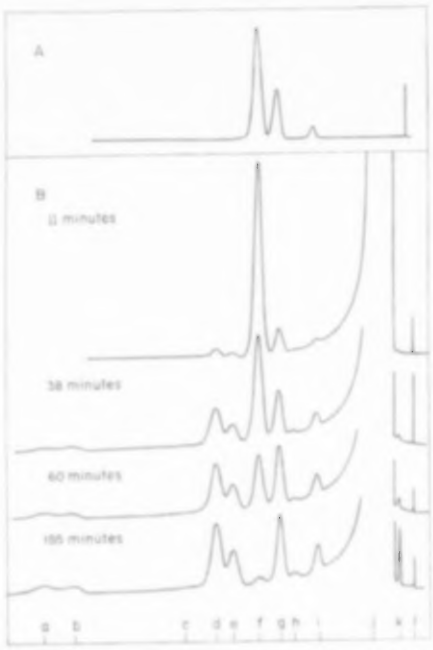


FIG. 1. A, v-p-c of chloride mixture from reaction of thionyl chloride with cyclopropylcarbinol; B, v-p-c of mixtures from solvolysis of cyclopropylcarbinyl chloride in 80% ethanol at 97° showing the change of composition with time. Peaks were identified as: a, cyclobutanol; b, cyclopropylcarbinol; c, allylcarbinol; d, cyclopropylcarbinyl ethyl ether; e, cyclobutyl ethyl ether; f, cyclopropylcarbinyl chloride; g, cyclobutyl chloride; h, allylcarbinyl ethyl ether; i, allylcarbinyl chloride; j, solvent; k, hydrogen chloride; l, air.

this reaction and the solvolysis of cyclobutyl chloride. A few microliters of standard solutions of the chlorides in 80 per cent aqueous ethanol were sealed into melting point capillaries, heated to 97° for various periods, and then small samples of the intact reaction mixtures analyzed by v-p-c. The accuracy of the analyses was at first somewhat limited by lack of reproducibility of the size of the sample injected into the v-p-c apparatus, but this difficulty was surmounted by incorporating a few per cent of cyclohexane in the reaction mixture to act as an internal standard. The added cyclohexane made no discernible change in the results except to permit considerably greater analytical precision. Since the supply of Mazur's high-purity chloride was limited, we used a somewhat less pure material (96 per cent cyclopropylcarbinyl, 2 per cent cyclobutyl, and 2 per cent allylcarbinyl chlorides) prepared from cyclopropylcarbinol and thionyl chloride in ether in the presence of tri-n-butylamine.[9,*]

* This reaction, when carried out with crotyl alcohol, gives no allylic rearrangement.

[8] R. H. DeWolfe and W. G. Young, *Chem. Rev.* **56**, 815 (1956); F. F. Caserio, Jr., Ph.D. Thesis, U.C.L.A. (1954).

The v-p-c tracings for typical solvolysis mixtures of I in 80 per cent ethanol are shown in Fig. 1B. The substances responsible for the various v-p-c peaks were assigned, by comparison of retention times, with those established for known samples. It is clear that solvolysis under these circumstances yields a variety of rearrangement products as chlorides, alcohols, and ethyl ethers. Fig. 2 shows the progress of the reaction as measured by the proportions of the various products formed. Again we conclude that solvolysis and rearrangement are intimately related.

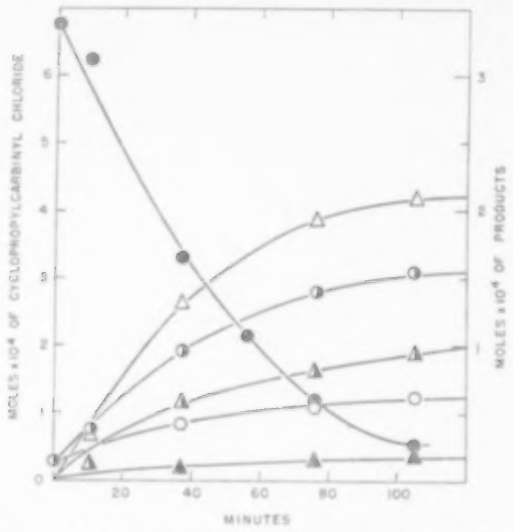


FIG. 2. Rate of change in composition of the mixture from the solvolysis of cyclopropylcarbinyl chloride in 80% ethanol at 97°: ● cyclopropylcarbinyl chloride, ◑ cyclobutyl chloride, ○ allylcarbinyl chloride, △ cyclopropylcarbinyl ethyl ether, ▲ cyclobutyl ethyl ether, ▲ allylcarbinyl ethyl ether. Cyclopropylcarbinol, cyclobutanol and allylcarbinol are also formed in small amounts but their formation is not shown.

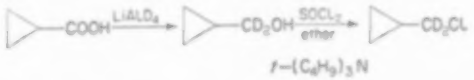
Weight has been added to the argument[4] for intervention of a common intermediate(s) in solvolysis reactions of cyclopropylcarbinyl and cyclobutyl chlorides by evidence for close similarity (in energy, at least) of the solvolysis transition states for these chlorides with the aid of the procedure discussed by Winstein and Kosower[10]. Thus, isomerization of cyclopropylcarbinyl chloride with zinc chloride at 25° gives a mixture of cyclobutyl-cyclopropylcarbinyl chlorides, the approximate equilibrium composition of which was determined by v-p-c as about 36/1 in favor of cyclobutyl chloride. The ratio of the total rates of disappearance of the chlorides (solvolysis plus internal-return isomerization) in 80 per cent ethanol at 97° is $1{\cdot}37 \times 10^{-5}$ $sec^{-1}/4{\cdot}17 \times 10^{-4}$ sec^{-1} equal to 1/30. Assuming that the equilibrium and relative rate data are not subject to large changes with change of media and temperature, the conclusion follows that the difference in rates between the two chlorides is not due to differences in transition-state stabilities but to differences in ground-state stabilities.*

* This possibility was suggested previously[1] but not given appropriate emphasis partly because no adequate data for the equilibrium composition was available.

[10] S. Winstein and E. M. Kosower, *J. Amer. Chem. Soc.* **81**, 4399 (1959); see also, E. F. Cox, Ph.D. Thesis, California Institute of Technology (1955).

The isomerization of cyclopropylcarbinyl chloride to cyclobutyl and allylcarbinyl chlorides induced by ionizing solvents is an excellent example of an interconversion reaction occurring under exceptionally mild conditions. Considerable interest is therefore attached to the degree of isotope-position rearrangement which accompanies this process. Some information bearing on this point has been obtained by deuterium-labeled chloride as follows.

First of all, the synthesis of cyclopropylcarbinyl chloride labeled with deuterium in the α-position presented a considerable problem. It was known from Mazur's[1] work that the reaction of cyclopropylcarbinol with thionyl chloride, with or without pyridine, gives a mixture of isomeric chlorides which cannot be separated conveniently. Allylic alcohols behave similarly under these conditions. However, chlorides may be prepared from primary allylic alcohols and thionyl chloride without rearrangement[9] if the reaction is carried out under carefully controlled conditions in the presence of an equivalent amount of tri-n-butylamine in ether or pentane solution. Using these conditions, a typical product obtained from cyclopropylcarbinol was found to consist of 91 per cent cyclopropylcarbinyl chloride, 8 per cent cyclobutyl chloride, and 1 per cent allylcarbinyl chloride. Clearly, the propensity for rearrangement in this system is high even under mild conditions known to give no rearrangement with allyl derivatives. Despite this, the method was used reasonably successfully for the preparation of deuterium-labeled cyclopropylcarbinyl chloride as shown in the following scheme:



The nuclear magnetic resonance (NMR) spectra of cyclopropylcarbinyl and cyclopropylcarbinyl-α-$^2H_2$ chlorides are shown in Figs. 3A and 3B, respectively. The characteristic doublet of the carbinyl protons is barely evident in the labeled chloride, and it is estimated that less than 4 per cent isotopic rearrangement occurred during its formation. This estimate was made from the peak area of the carbinyl protons relative to the tertiary ring proton which, of course, is assumed to be 2:1 in the unlabeled chloride.

In an attempt to observe isotope-position rearrangement during hydrolysis, a sample of cyclopropylcarbinyl-α-$^2H_2$ chloride (containing 6 per cent cyclobutyl chloride) was shaken with water in a sealed tube at 97°. After 140 minutes, the unreacted chloride was separated from the aqueous layer and analyzed by v-p-c. The ratio of chlorides, cyclopropylcarbinyl:cyclobutyl:allylcarbinyl, was found to be 7·5:3·2:1·0, respectively. The hydrolysis products remained largely in aqueous solution, but small amounts of alcohols (and water) were also present in the chloride mixture. The NMR spectra of this mixture and that obtained from unlabeled chloride under the same conditions are shown in Figs. 3C and 3D, respectively. The incidence of isotopic rearrangement is evident from Fig. 3C, which shows a sharp doublet due to the carbinyl protons of cyclopropylcarbinyl chloride, the spectrum of which was barely evident initially (cf. Fig. 3B). Unfortunately, the complexity of the spectrum precluded a *precise* measurement of how much rearrangement of the deuterium label had occurred. However, it is estimated from the ratio of peak areas of the carbinyl and tertiary cyclopropylcarbinyl protons that some 24 per cent of isotopically

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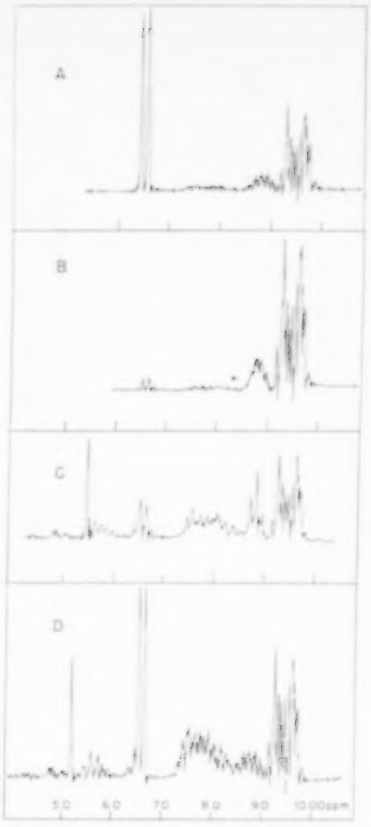


FIG. 3. NMR spectra at 60 mc in ppm relative to tetramethylsilane as internal standard (equal to 10 ppm). A, cyclopropylcarbinyl chloride from photochlorination of methylcyclopropane;[1] B, cyclopropylcarbinyl-α-$^2H_2$ chloride from cyclopropylcarbinol-α-$^2H_2$ and thionyl chloride in ether and tri-n-butylamine; C, chloride mixture from hydrolysis of cyclopropylcarbinyl-α-$^2H_2$ chloride; D, chloride mixture from hydrolysis of cyclopropylcarbinyl chloride.

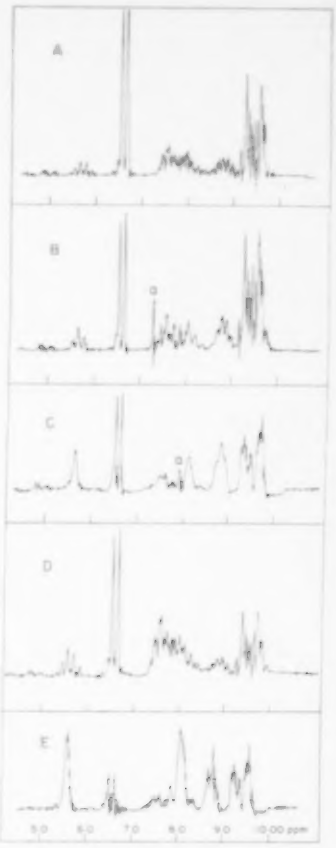


FIG. 4. NMR spectra at 60 mc in ppm relative to tetramethylsilane as internal standard (equal to 10 ppm) of chloride mixtures obtained from reaction of thionyl chloride with: A, cyclopropylcarbinol or cyclobutanol; B, cyclopropylcarbinol-α-$^2H_2$, peak marked *a* is impurity; C, cyclobutanol-2,4-$^2H_4$, peaked marked *a* is impurity; D, cyclobutanol in presence of tri-n-butylamine and ether; E, cyclobutanol-2,4-$^2H_4$, conditions as in C.

rearranged cyclopropylcarbinyl chloride is present in the mixture. Further evidence for isotope-position rearrangement was obtained from other related reactions which we now describe.

It was originally observed by Mazur that chloride mixtures of the *same* composition were obtained from the reaction of cyclopropylcarbinol and cyclobutanol with thionyl chloride (no solvent). We have repeated these reactions with deuterium-labeled alcohols, using the conditions defined by Mazur, in order to observe the extent of isotope-position rearrangement in the chloride mixtures by means of NMR. The labeled alcohols required for these experiments were prepared as follows. Cyclopropylcarbinol-α-$^2H_2$ was prepared by the reduction of cyclopropanecarboxylic acid

with lithium aluminum deuteride. To obtain deuterium-labeled cyclobutanol, cyclobutanone-2,4-$^2H_4$ was prepared to about 95 per cent isotopic purity by base-catalyzed exchange of cyclobutanone in deuterium oxide and the product was subsequently reduced to the alcohol with lithium aluminum hydride. The NMR spectrum of the crude labeled ketone is shown in Fig. 6C and may be compared to the

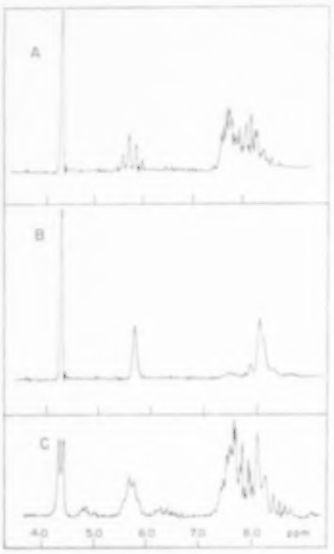


FIG. 5. NMR spectra at 60 mc in ppm relative to tetramethylsilane as internal standard (equal to 10 ppm). A, cyclobutanol from acid-catalyzed rearrangement of cyclopropylcarbinol; B, cyclobutanol-2,4-$^2H_4$; C, deuterium-labeled cyclobutanol from acid-catalyzed rearrangement of cyclopropylcarbinol-α-$^2H_2$(allylcarbinol is also present in small amounts).

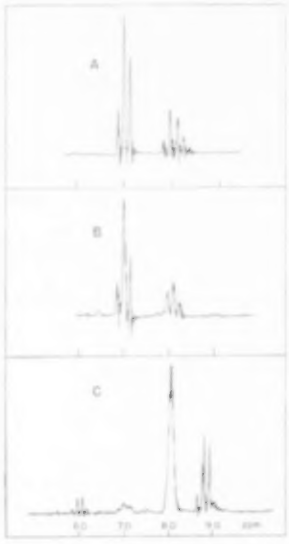
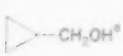
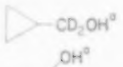
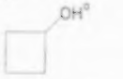
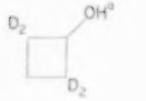
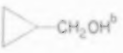
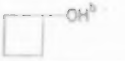


FIG. 6. NMR spectra at 60 mc in ppm relative to tetramethylsilane as internal standard (equal to 10 ppm). A, cyclobutanone; B, deuterium-labeled cyclobutanone from oxidation of labeled cyclobutanol (minor peaks are due to impurities); C, cyclobutanone-2,4-$^2H_4$ (impure).

spectrum of unlabeled cyclobutanone in Fig. 6A. The spectrum of the labeled ketone was run at high gain in order to detect any residual protonation of the 2 and 4 positions. The presence of significant amounts of impurities is apparent, but it is also evident that there remains only 4–5 per cent of ketone with protons in the 2 or 4 positions. The spectra of cyclobutanol and cyclobutanol-2,4-$^2H_4$ are shown in Figs. 5A and 5B, respectively. The 3-methylene protons of the labeled alcohol appear as a rather indistinct quartet since these two protons are non-equivalent; the 4–5 per cent of 2- or 4-protonated material appears on the low field side of this quartet.

The composition of the chloride mixtures from the thionyl chloride reaction was determined by v-p-c. The results are shown in Table 1 and, clearly, they confirm that the *same* mixture of chlorides is obtained from either alcohol. The NMR spectra corresponding to the chloride mixtures obtained from cyclopropylcarbinol (or cyclobutanol), cyclopropylcarbinol-α-$^2H_2$, and cyclobutanol-2,4-$^2H_4$ are shown respectively in Figs. 4A, 4B and 4C. They are exceedingly complex, and it was not possible to determine the distribution of the deuterium label within the cyclobutyl ring with certainty. However, by focusing attention on the sharp doublet of the carbinyl protons

TABLE 1. PERCENT COMPOSITION OF CHLORIDE MIXTURES FROM REACTION OF THIONYL CHLORIDE WITH CYCLOPROPYLCARBINOL AND CYCLOBUTANOL

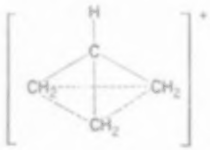
Alcohol	Cyclopropylcarbinyl	Cyclobutyl	Allylcarbinyl
	%	%	%
	69	27	4
	67	28	5
	69	25	6
	67	29	4
	~67	~30	~3
	~67	~30	~3

[a] Analyzed by v-p-c.
[b] Analyzed by infrared spectrometry.[1]

of cyclopropylcarbinyl chloride, one thing becomes immediately apparent—in order for this doublet to appear at all, extensive isotope-position rearrangement must have occurred during the formation of cyclopropylcarbinyl chloride from both deuterium-labeled alcohols. Moreover, the area of this doublet relative to the area of the tertiary ring hydrogen of cyclopropylcarbinyl chloride permits a rough estimate of the percent isotopic rearrangement to be made. Such measurements reveal that 66 $\pm$ 5 per cent of the cyclopropylcarbinyl chloride obtained from cyclopropylcarbinol-α-$^2H_2$ has a —CH_2— group in the α-position, while 33 $\pm$ 2 per cent of the chloride from cyclobutanol-2,4-$^2H_4$ has a —CH_2— group in the α-position. These figures closely approach the values of 67 per cent and 33 per cent, respectively, for a statistical distribution of the deuterium label in cyclopropylcarbinyl chloride derived from both labeled alcohols. Thus, the three methylene groups of cyclopropylcarbinol and cyclobutanol achieve near equivalence during reaction—a result which, in conjunction with the identity of product composition, argues for formation of the same cationic intermediates from either alcohol. As a check on the validity of area measurements, the ratio of cyclopropylcarbinyl chloride to the cyclobutyl chloride present was estimated from the ratio of peak areas of the tertiary proton of each chloride. The results gave a ratio of cyclopropylcarbinyl to cyclobutyl of 2·28 $\pm$ 0·12 and 2·26 $\pm$ 0·19 for the chlorides from labeled cyclopropylcarbinol and cyclobutanol, respectively (cf. Figs. 3B and3C), while analysis by v-p-c gave the ratio as 2·3 (cf. Table 1). The agreement is satisfactory.

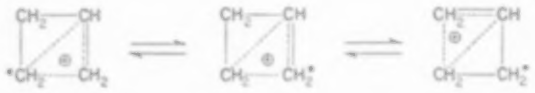
On treating these same alcohols with thionyl chloride in the presence of tri-n-butylamine in a non-ionizing solvent (ether or pentane) somewhat different results were obtained as already discussed in the case of cyclopropylcarbinol. Under these conditions, cyclobutanol reacted with extensive rearrangement to give 45 per cent cyclopropylcarbinyl, 50 per cent cyclobutyl, and 5 per cent allylcarbinyl chlorides.

The NMR spectrum of the mixture is shown in Fig. 4D. If one assumes that the product distribution arising from carbonium ion intermediates is the same as that obtained in the absence of added base and solvent (cf. Table 1), then it may be estimated that 66 per cent of reaction takes an ionic path with rearrangement and 34 per cent proceeds without rearrangement probably by an S_N2 displacement.[9] The NMR spectrum of the chloride mixture from cyclobutanol-2,4-$^2H_4$ (Fig. 4E) is especially interesting since it shows that only 16·5 ± 1 per cent of the —CH_2— group turns up in the α-position of cyclopropylcarbinyl chloride. Again, the area measurements were judged to be significant since the ratio of cyclopropylcarbinyl chloride to cyclobutyl chloride was determined as 1·03 ± 0·10 by NMR and 0·9 by v-p-c. In this case then, the extent of isotopic rearrangement is about one half that expected for complete equilibration of the three methylene groups. This result is highly significant in that it rules out the possibility of a symmetrical ion such as III as the sole intermediate in these interconversion reactions. The methylene groups are completely equivalent in III, which inevitably would lead to products with a random isotope distribution under any set of reaction conditions. A similar conclusion was reached from the results of nitrous-acid deamination of cyclopropylcarbinylamine-α-$^{14}C^4$. The ^{14}C-distribution in the products, cyclopropylcarbinol and cyclobutanol, showed that extensive but not random ^{14}C-rearrangement had taken place. It was suggested that these results could



III

best be explained by the intermediacy of the unsymmetrical bicyclobutonium ions IIa, IIb, and IIc, which equilibrate rapidly but not instantaneously. Clearly, the present results can be rationalized by these same intermediates. The advent of less isotopic



IIa IIb IIc

rearrangement in the reaction of cyclobutanol with thionyl chloride when carried out in the presence of tri-n-butylamine in ether solution is indicative that equilibration of IIa–c is not fully attained in this medium. Under the best ionizing conditions, when the alcohol acts as its own solvent, equilibration is attained more rapidly and results in a more nearly random isotope distribution.

Cyclopropylcarbinol has been found to undergo a facile rearrangement in dilute aqueous acid to give cyclobutanol and small amounts of allylcarbinol.* The rearrangement, which provides an excellent synthetic route to cyclobutanol, has been studied with the aid of cyclopropylcarbinol-α-$^2H_2$, and it was hoped that the position of the deuterium label in the resulting cylcobutanol could be observed from its NMR

* This rearrangement was first observed by Mr. David I. Schuster in these Laboratories.

spectrum. Unfortunately, the spectrum of the product turned out to be too complex to interpret (Fig. 5C). To overcome this, the labeled cyclobutanol was oxidized to cyclobutanone with chromic oxide in pyridine, and the distribution of deuterium was observed from the NMR spectrum of the cyclobutanone which is relatively simple. The spectra obtained for both labeled and unlabeled cyclobutanones are shown in Figs. 6A and 6B, respectively. The presence of 2-labeled cyclobutanone in the rearrangement product is clearly evident from Fig. 6B since the five-line spectrum of the 3-methylene protons in the unlabeled ketone is reduced to a broad triplet in the labeled material. Equally clear is the presence of 3-labeled cyclobutanone since the triplet due to the 2-methylene protons has a central peak of far greater intensity than in the unlabeled ketone. Thus, the deuterium label is found in all three methylene groups of the ring. The relative amounts of 2- and 3-labeled cyclobutanones may be roughly calculated from relative peak areas. The area of the 2- and 4-protons relative to the 3-protons was measured as 2·1 ± 0·1, which gives the composition of the mixture as 67 per cent cyclobutanone-2-$^2H_2$ and 33 per cent cyclobutanone-3-$^2H_2$. Consequently, it is inferred that cyclobutanol derived from cyclopropylcarbinol-α-$^2H_2$ has the deuterium-labeled methylene group statistically distributed between the 2,3- and 4-ring positions.

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EXPERIMENTAL

Cyclopropylcarbinol-α-$^2H_2$. (b.p. 121–122·5°, 746 mm) was prepared in 75% yield by the reduction of cyclopropanecarboxylic acid with lithium aluminum deuteride.

Cyclobutanol-2,4-$^2H_4$. A mixture of three parts of cyclobutanone to four parts of dueterium oxide, 0·1 M in sodium acetate, was heated in a sealed tube at 97° for 37 hr. The ketone was recovered from solution and similarly treated with fresh deuterium oxide, 0·1 M in sodium acetate. The crude, recovered cyclobutanone gave an NMR spectrum showing 95% deuterium in the 2- and 4-positions (Fig. 6C). This material was reduced with lithium aluminum hydride, and the crude product was fractionally distilled. The purest fraction of labeled cyclobutanol obtained which was used in subsequent experiments had b.p. 122·5–123·0° at 745 mm, $n_D^{25} = 1·4315$, and gave a single peak in the v-p-c. The NMR spectrum of this material is shown in Fig. 5B.

Cyclobutanol from cyclopropylcarbinol. A solution of cyclopropylcarbinol (30·0 g) in 280 ml water and 25 ml conc hydrochloric acid was heated on a steam bath for 100 min. Most of the acid was neutralized by the addition of 11·0 g sodium hydroxide pellets to the cooled mixture. Neutralization was completed with potassium carbonate. The mixture was continuously extracted with ether and the ether extracts were dried over magnesium sulfate, filtered, and the ether removed by distillation. The residue was distilled through a small wire spiral-packed column to give 21·6 g (72%) material, b.p. 121–124°, which analyzed by v-p-c as 97% cyclobutanol and 3% allylcarbinol.

By the above procedure, 5·33 g of cyclopropylcarbinol-α-$^2H_2$ gave 3·73 g (70%) deuterium-labeled material, b.p. 121·5–125°, which analysed by v-p-c as 93% cyclobutanol and 7% allylcarbinol.

Oxidation of deuterium-labeled cyclobutanol to cyclobutanone. The oxidizing agent employed was chromic oxide in pyridine, and the procedure was essentially that described by Poos *et al.*[11] To a stirred suspension of chromic oxide-pyridine complex in pyridine (5·0 g chromic oxide to 48 g pyridine) at 17° was added 3·53 g deuterium-labeled cyclobutanol (containing 7% allylcarbinol) in 32 g pyridine. The mixture was allowed to stand at room temp for about 18 hr. The pyridine was converted to the hydrochloride by the addition of 98 g conc hydrochloric acid in 100 g ice water to the ice-cooled mixture. The resulting solution was evaporated immediately *in vacuo* at room temp and the vapors condensed in a series of dry ice traps. The aqueous distillate was continuously extracted with ether and the ether extracts were dried over sodium sulfate and distilled. The crude product obtained was shown by v-p-c to consist of unreacted cyclobutanol, cyclobutanone, and small amounts of allylcarbinol. The cyclobutanone was separated from the alcohols by v.p.c. using a preparative column.

Thionyl chloride reactions. Thionyl chloride (1·65 g) was added dropwise to 1·0 g cyclopropylcarbinol at 0° with stirring. Evolution of sulfur dioxide immediately took place. The mixture was

[11] G. I. Poos, G. E. Ayth, R. E. Beyler and L. H. Sarett, *J. Amer. Chem. Soc.* **75**, 422 (1953).

allowed to stand at room temp for 3·5 hr. Dissolved hydrogen chloride was neutralized by the addition of a few drops of water and solid potassium carbonate. The chloride mixture was analyzed by v-p-c and then distilled. The product composition was found not to vary with reaction time; however, on working up the mixture immediately upon addition of thionyl chloride, some unrearranged cyclopropylcarbinol was recovered. Cyclopropylcarbinol-α-$^2H_2$, cyclobutanol, and cyclobutanol-2,4-$^2H_4$ were treated with thionyl chloride exactly as described for cyclopropylcarbinol.

To a well-stirred, ice-cooled mixture of 10·0 g (0·139 mole) of cyclopropylcarbinol, 25·4 g (0·139 mole) of tri-n-butylamine (b.p. 123° at 51 mm) in 200 ml ether was added 16·5 g (0·139 mole) of thionyl chloride at such a rate that the temp did not exceed 6°. The addition took about 80 min and the precipitate which formed during the addition eventually re-dissolved to give two liquid phases, one of which was orange-yellow in color. The volatile components were flash-distilled *in vacuo* and trapped at −78°. The ether was evaporated from the distillate and the residue, after analysis by v-p-c, was fractionally distilled. There was obtained overall 10·8 g (86%) material, b.p. 82·5–85·5° at 748 mm, of which 2·9 g had b.p. 85·5° and which analyzed for 97% cyclopropylcarbinyl chloride and 3% cyclobutyl chloride.

Cyclopropylcarbinyl-α-$^2H_2$ chloride was prepared by this method. On treating cyclobutanol and cyclobutanol-2,4-$^2H_4$ with thionyl chloride as described above, the reaction was found to be appreciably slower; it was necessary to leave the reaction mixture at room temp for 3 hr before flash-distilling the products. Shorter reaction times gave poor yields, yet the product composition remained unchanged.

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HEPTAFULVENE (METHYLENECYCLOHEPTATRIENE)[1]

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(*Received* 6 *May* 1960)

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Abstract—Heptafulvene (Chart 2, I), a conjugated, non-benzenoid hydrocarbon of theoretical interest, has been synthesized by a Hofmann elimination on trimethyl 7-cycloheptatrienylmethyl ammonium iodide. Non-isolable, stable only in dilute solution, I is assigned the heptafulvene structure on the basis of catalytic hydrogenation to methylcycloheptane; indication of a methylene group from I. R. and ozonolysis to formaldehyde; association of elaborate visible and U. V. spectrum with a highly conjugated system; marked sensitivity to acid; and reaction with acetylene dicarboxylic ester to give (ultimately) an azulene derivative.

"NON-BENZENOID AROMATIC"[3] defines a class of conjugated, *cyclic* olefins which may be substituted *ad libitum*, and may have, in theory, a lower energy content (a greater π-electron delocalization energy) than their apposite *acyclic* analogues.[4] It is in such systems of coplanar conjugated double bonds that the efforts of theoreticians to simplify the otherwise prohibitively complicated quantum mechanical analysis of larger molecules have met with success.[6–9]

The interest of organic chemists stems from a traditional concern with the synthesis of new types of molecules and a natural desire to make available for experimental examination substances, the properties of which have, in part, already been anticipated by theoretical analysis. The promise of substantial π-electron delocalization energy in many of the hypothetical systems has been hopefully equated with a chemical stability beyond the ordinary[10] and has aroused a particular enthusiasm among organic chemists.

The theory of aromatic character changed from the empirical generalization of

[1] This work is taken from a dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Faculty of the Graduate School of Yale University, May, 1955. Preliminary announcements are to be found in Abstracts of Papers presented at the 126th Meeting of the American Chemical Society, New York, N.Y., 12 September 1954, p. 10–0 and *Angew. Chem.* 67, 429 (1955). See also *Theoretical Organic Chemistry* pp. 41–44. Butterworths, London (1959).

[2] We acknowledge gratefully the support of the Office of Ordnance Research, United States Army, in the form of contract DA-19-059-ORD-1562 with Yale University.

[3] W. Baker and J. W. F. McOmie in J. W. Cook, *Progress in Organic Chemistry* Vol. III, p. 44. Butterworths, London (1955).

[4] In extending the definition to include conjugated *acyclic* molecules, Dauben[5] jeopardizes the very bound on which its usefulness depends.

[5] H. J. Dauben, Abstracts of Papers presented at 126th Meeting of the American Chemical Society, New York, N.Y., 12 September 1954, p. 18–0.

[6] E. Hückel, *Grundzüge der Theorie ungesättigter und aromatischer Verbingungen.* Verlag Chemie, Berlin (1938).

[7] B. Pullman and A. Pullman, *Les Theories Electronique de la Chimie Organique.* Masson et Cie, Paris (1952).

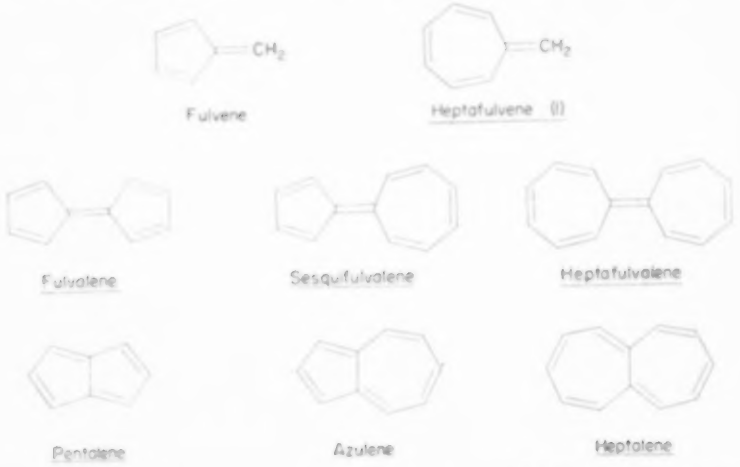
[8] C. A. Coulson, *Valence.* Oxford University Press, Oxford (1951).

[9] Y. K. Syrkin and M. E. Diatkina, *Structure of Molecules and the Chemical Bond.* Butterworths, London (1950).

[10] The association of "π-electron delocalization energy" with such characteristics as "stability," "aromaticity" and "reaction by substitution" is based on analogy with traditional benzenoid aromatic chemistry and has no general theoretical justification. Stability depends on the difference in free energy between that of the starting molecules and that of the transition state for the hypothetical chemical change. Knowledge or predictions of the free energy of the starting system alone cannot define the necessary difference.

the "rule of six"[11] to the modern quantum mechanical description when E. Hückel[6] in 1931 developed the molecular orbital method of calculating the energies of π-electrons in planar systems of double bonds. The aromatic character of benzene was reflected in an "experimental" stabilization energy and a theoretically calculable π-electron delocalization energy. The remarkable properties of Thiele's[12] cyclopentadienide anion found satisfactory theoretical explanation. The existence of a positively charged, seven-membered cycle as a relatively stable carbonium ion was predicted and established several years later by the discovery of the water-soluble, stable tropylium ion.[13] Instead of one, three aromatic systems emerged: the pentagonal system with the anionic cyclopentadienide ion as its parent, the neutral benzene (or hexagonal) system and the heptagonal system headed by the cationic cycloheptatrienylium ion. References to members of the pentagonal family are to be found in a recent paper by Lloyd and Sneezum[14], while a reasonably detailed view of the heptagonal family can be obtained from articles by Pauson[15] and Doering and Krauch[16].

In the years following Hückel's pioneering work, the molecular orbital theory was elaborated and applied to many novel, unknown systems of conjugated double bonds. Among these, the simple mono- and dicyclic systems of five- and seven-membered rings fell quite naturally into a group of eight: fulvene and heptafulvene (I); fulvalene, sesquifulvalene and heptafulvalene; and pentalene, azulene and heptalene. At the start of this work, eight years ago, only two of the eight systems



were known: the fulvene type which had long been recognized in its many derivatives[17] (although only recently free of substituents[18]) and the azulene type, long a center of

[11] See W. Hückel, *Theoretische Grundlagen der organischen Chemie* (5th Ed.), Vol. I, pp. 507–524. Akademische Verlag, Leipzig (1944).
[12] J. Thiele, *Ber. Dtsch. Chem. Ges.* **33**, 666 (1900); *Liebigs Ann.* **319**, 226 (1901).
[13] W. von E. Doering and L. H. Knox, *J. Amer. Chem. Soc.* **76**, 3203 (1954).
[14] D. Lloyd and J. S. Sneezum, *Tetrahedron* **3**, 334 (1958).
[15] P. L. Pauson, *Chem. Rev.* **55**, 9 (1955).
[16] W. von E. Doering and H. Krauch, *Angew. Chem.* **68**, 661 (1956).
[17] J. H. Day, *Chem. Rev.* **53**, 167 (1953); E. D. Bergmann, *Progress in Organic Chemistry* Vol. III, p. 81. Butterworths, London (1955).
[18] J. Thiec and J. Wiemann, *Bull. Soc. Chim. Fr.* 177 (1956).

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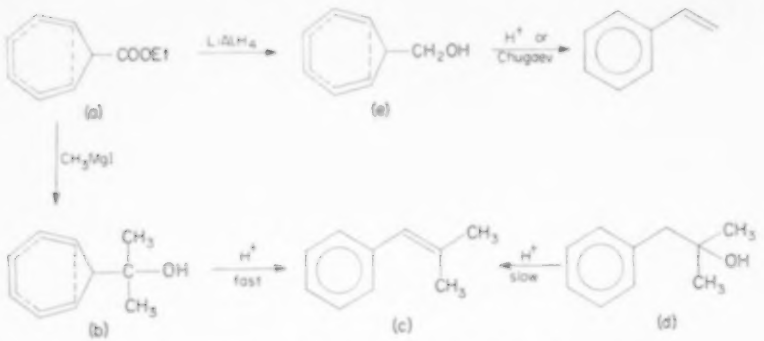
intense activity and interest.[19] In this and two papers to follow, the first syntheses of three more of the eight, **heptafulvene** (I), **heptafulvalene** and **fulvalene,** are described.

Heptafulvene (I) was first treated theoretically by Berthier and Pullman in 1949[20] by the molecular orbital (LCAO) and the valence bond methods. π-Electron delocalization energies of 1·994 β ($\beta_{benzene}$ = 18 kcal/mole; S = 1) and 0·779 γ ($\gamma_{benzene}$ = 34 kcal/mole; S = 0·25) were calculated by the former method and 0·57 α ($\alpha_{benzene}$ = 33 kcal/mole) by the latter. More refined calculations[21] based on Wheland and Mann[22], predicted a π-electron delocalization energy of 0·46 γ. The simple MO (LCAO) method predicts a dipole moment of 4·6 D[20] with the ring positive, while the refined method predicts 0·85 D in the same direction.[21] Calculations by the self-consistent field method of Roothaan leads to a small dipole moment (0·14 D) in the opposite direction,[23] while use of the Pariser–Parr method gives a value of 0·6 D, again in the direction of the ring positive. Calculations of the predicted light absorption have also been made.[21–24]

The only published report on the attempted synthesis of heptafulvene is by Grundmann *et al.*[25] and describes failures to effect the synthesis by the elimination of water from α-, β- and γ-cycloheptatrienyl-carbinols and dimethylcarbinols. Our initial approach, equally abortive, involved the corresponding carbinols in the so-called "norcaradiene" series (Chart 1: B and E). All the contributors to the Buchner acid problem had, up to that time, agreed in assigning the "norcaradiene" structure to the parent acid and the 7-cycloheptatrienyl arrangement to other acids—Buchner to the γ,[26] De Jong to the γ[27] and Grundmann and Ottmann to the α[28] Firmly convinced that the "norcaradiene" and "7-cycloheptatriene" carboxylic acid arrangements could not represent more than a single substance between them, we worked exclusively with the "norcaradiene" series, content to attribute failures to factors other than incorrect choice of starting material. Later, it was shown[29,30] that the α- and γ-acids were the 2- and 1-cycloheptatrienyl carboxylic acids, that the δ-acid did not exist[29] and that the so-called Buchner or "norcaradiene" carboxylic acid was most probably the 7-cycloheptatrienyl carboxylic acid.[29,31,32]

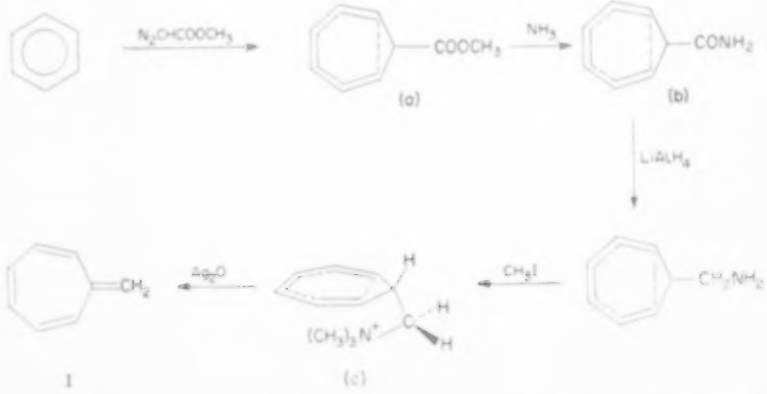
The reaction of ethyl "norcaradiene" carboxylate (Chart 1, A) with methylmagnesium iodide produced the crystalline dimethyl-7-cycloheptatrienylcarbinol (Chart 1, B) which rearranged exothermically to β,β-dimethylstyrene (Chart 1, C) on acid-catalyzed dehydration.[33]

[19] F. Gordon, *Chem. Rev.* **50**, 127 (1952); K. Hafner, *Angew. Chem.* **70**, 419 (1958); see also the first two pages of D. H. Reid, *Tetrahedron* **3**, 337 (1958).
[20] G. Berthier and B. Pullman, *Trans. Faraday Soc.* **45**, 484 (1949).
[21] E. D. Bergmann, E. Fischer, D. Ginsburg, Y. Hirshberg, D. Lavie, M. Mayot, A. Pullman and B. Pullman, *Bull. Soc. Chim. Fr.* **18**, 684 (1951).
[22] G. E. Wheland and D. E. Mann, *J. Chem. Phys.* **17**, 246 (1949).
[23] A. Julg, *J. Chim. Phys.* **52**, 50 (1955).
[24] A. Julg and B. Pullman, *J. Chim. Phys.* **52**, 481 (1955).
[25] Ch. Grundmann, G. Ottmann and G. Gollmer, *Liebigs Ann.* **582**, 178 (1953).
[26] E. Buchner, *Ber. Dtsch. Chem. Ges.* **31**, 2241 (1898).
[27] A. W. K. De Jong, *Rec. Trav. Chim.* **56**, 198 (1937).
[28] Ch. Grundmann and G. Ottmann, *Liebigs Ann.* **582**, 163 (1953).
[29] W. von E. Doering, G. Laber, R. Vonderwahl, N. F. Chamberlain and R. B. Williams, *J. Amer. Chem. Soc.* **78**, 5448 (1956).
[30] K. Alder, H. Jungen and K. Rust, *Liebigs Ann.* **602**, 94 (1956).
[31] In addition to having been largely responsible for the failure of Grundmann *et al.*[25], the incorrectness of the earlier structural assignments to the Buchner acids appears also to have sabotaged at least one attempted tropylium ion synthesis. Cf. footnote 8 in M. J. S. Dewar and R. Pettit, *J. Chem. Soc.* 2021 (1956).
[32] See also M. V. Evans, Jr. and R. C. Lord, Abstracts of Papers presented at the 135th Meeting of the American Chemical Society, Boston, Massachusetts, 5 April 1959, p. 64R.
[33] C. R. Ganellin and R. Pettit, *J. Chem. Soc.* 576 (1958) have effected the same transformations independently.



The contrast between the remarkable exothermicity of this dehydration-rearrangement and the (qualitatively) thermoneutral dehydration of the isomeric dimethylbenzylcarbinol (Chart 1, D), both to the same product, is one of the few instances where the liberation of the resonance energy of benzene is easily palpable. Attempts to convert 7-cycloheptatrienyl-carbinol (Chart 1, E) to heptafulvene (I) were also unsuccessful: dehydration by acid-catalyzed elimination and by the Chugaev sequence (generally considered to be a non-acidic mode of dehydration) led to styrene.

Hoping that milder, but still strongly alkaline, conditions might permit retention of the cycloheptatriene system during the introduction of the fourth double bond, we turned to the Hofmann elimination (Chart 2). The starting material, 7-cycloheptatrienylcarboxamide (Chart 2, B: Buchner's "norcardienyl" carboxamide), is prepared more quickly, in better yield and in a higher state of purity from *methyl* 7–cycloheptatrienyl carboxylate (Chart 2, A) than from the ethyl ester. If the structure of the amide follows from its method of preparation and from its saponification to 7-cycloheptatrienyl carboxylic acid. The reduction of the amide with lithium aluminum hydride at room temperature gives a mixture of amines which can be converted to a mixture of the corresponding trimethyl ammonium iodides. It is



convenient to effect purification at this point, although a tedious fractional crystallization is required to separate the desired trimethyl 7-cycloheptatrienylmethyl ammonium iodide from a dihydro derivative. The formation of the dihydro derivative can be diminished substantially by carrying out the reduction at 0°. The ultraviolet

spectrum of trimethyl 7-cycloheptatrienyl ammonium iodide (Chart 2, C) has (after compensation for absorption by iodide ion) a maximum at 255 mμ (log ε 3·53). On the basis of essential identity of this spectrum with that of the preceding 7-cycloheptatrienylmethylamine (λ_{max} 253; log ε 3·51) and the starting 7-cycloheptatrienylcarboxamide (λ_{max}258; log ε 3·47), it is concluded that no change in ring structure has occurred during the reduction and exhaustive methylation.

The Hofmann elimination of trimethylamine from C (Chart 2) must be effected in a special way because of the extreme instability of heptafulvene (I). An aqueous solution of the trimethylammonium hydroxide is prepared in the usual manner with excess of silver oxide and is concentrated *in vacuo* at 25° to a thick oil, whereupon decomposition sets in. A trap either empty or containing a solvent, is connected and cooled to −70°. The decomposition is then completed *in vacuo* in a water bath at 50° as rapidly as possible. In the absence of solvent, a red film condenses which can be saved by dissolving in cold solvent within a minute or so, but which otherwise changes quickly to a colorless polymer. In the presence of solvent, the vapors dissolve at once to give deep red solutions of heptafulvene with the formation of little or no polymer. It is noteworthy that the product has been purified once by distillation in the course of the preparation itself.

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Heptafulvene cannot be isolated; at least, trapping at −170°, extracting with propane and concentrating *in vacuo* at −60° gives only colorless polymer. On concentration, a distillable, perhaps dimeric, material is produced first, but it rapidly polymerizes further. Even dilute solutions of I are not indefinitely stable. A 0·03 M solution in hexane from which trimethylamine has been removed by washing wih water shows appreciable decomposition within an hour at −60°, whereas a 0·003 M solution is essentially unchanged in this time. Appreciable stabilization is effected by trimethylamine or the use of ethers as solvent. Thus, a 0·02 M solution in tetrahydrofuran from which trimethylamine has not been removed retains half the original material after four days at room temperature.

The task of proving the structure of heptafulvene (I) and of gaining information about its chemical and physical properties has been made difficult and often frustrating by the instability of the substance and by the need at all times to work in dilute solution.

A striking feature of heptafulvene is its absorption spectrum in the ultraviolet and visible region, shown in Fig. 1. In this elaborate spectrum, two broad bands are discernible, one with its most intense absorption at 279 mμ (35,850 cm^{-1}; 4·44 eV) and the other with its maximum absorption at 427 mμ (23,450 cm^{-1}; 2·90 eV). The spectrum is surely indicative of a highly unsaturated, conjugated system.[34]

The extinction coefficients could be determined with only limited precision because of uncertainties in the determination of concentration. By assuming a quantitative yield in the best of several preparations, a minimum value for the extinction coefficient at 426 mμ (in tetrahydrofuran as solvent) of 300 was found. By hydrogenating a hexane solution, concentrating, chromatographing in pentane, concentrating, adding carbon tetrachloride and concentrating again, it was possible to determine the final amount of methylcycloheptane (35·5 per cent of theory). Based on the assumption

[34] Cyclooctatetraene is far from planar and yet possesses an extensive absorption spectrum (Am. Pet. Inst. Res. Proj. 44, Ultraviolet Spectrul Data, Serial No. 180). Although this example serves as a general caution to concluding that absorbing conjugated systems are essentially planar, it does not weigh very heavily in the present case because of the much greater intensity and range of absorption of heptafulvene.

of quantitative reduction, an extinction coefficient of 490 is calculated. This is a maximum value because some methylcycloheptane must have been lost by codistillation during the isolation procedure. An intermediate and probably most reliable value of 370 is obtained on the basis of the quantitative determination of hydrogen absorption (in Diethyl Carbitol as solvent) obtained during measurements of the heat of hydrogenation.[35]

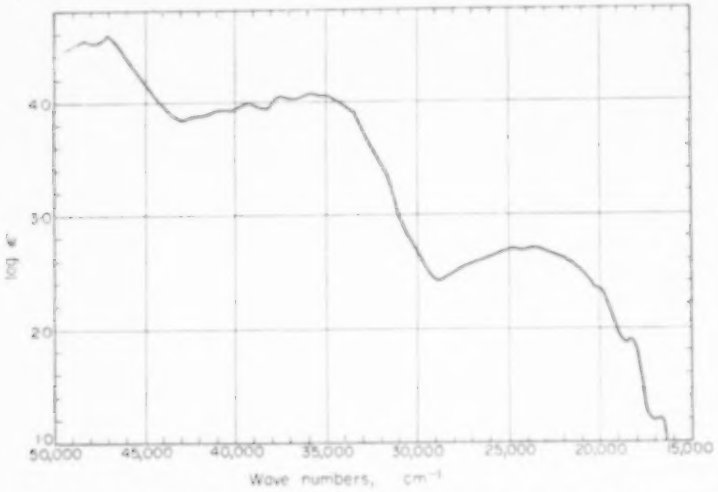


FIG. 1. Ultraviolet and visible absorption spectrum of heptafulvene (I) in n-hexane solution

The isolation of methylcycloheptane from the catalytic reduction may be taken as strong evidence that no rearrangement of carbon skeleton occurred during the Hofmann elimination. Barring sequences such as rearrangement to 1-cycloheptatrienylmethyl trimethyl ammonium ion and elimination to allyilidenemethylenecyclobutene, one might have expected styrene as the product of a completely concerted elimination from the valence tautomeric 7-norcaradienylmethyl trimethyl ammonium ion. In this connection, it is relevant that an anti-parallel configuration is available to the 7-cycloheptatrienylmethyl ammonium ion (Chart 2, C).

The presence of the methylene group in heptafulvene is indicated by the isolation of formaldehyde in low yield on ozonolysis. Confirmation is found in the infrared spectrum. Solutions of heptafulvene are concentrated quickly to ca. 1 per cent at which time they are deep-red and short-lived. Infrared spectra are taken as rapidly as possible and compared with the spectra of the same solutions measured two hours later, after the heptafulvene has completely disappeared. Among the bands listed in the experimental section, strong bands at 6·31 μ (1585 cm^{-1}) and at 11·75 μ (852 cm^{-1}) are attributable to the exocyclic methylene group. Sheppard and Simpson[36] find 1650 $\pm$ 11 cm^{-1} (medium) and 889 $\pm$ 3 cm^{-1} (strong) for the double-bond stretching and carbon-hydrogen out-of-plane wagging modes of aliphatic unsymmetrically disubstituted olefins. The shift to lower energies and stronger intensities is to be expected of the absorptions of the methylene group in heptafulvene. In this molecule,

[35] R. B. Turner, W. R. Meador, W. von E. Doering, L. H. Knox, J. R. Mayer and D. W. Wiley, *J. Amer. Chem. Soc.* **79**, 4127 (1957).
[36] N. Sheppard and D. M. Simpson, *Quart. Rev.* **6**, 1 (1952).

the anticipated dipole moment could lead to an intensification of the stretching mode and a weakening of the methylene-carbon bond.

A reaction simulant of a Diels–Alder occurs between heptafulvene and dimethyl acetylene dicarboxylate. Although less reactive dienophiles have no effect on heptafulvene, this one reacts in a period of days to give a colorless adduct (Chart 3, B). Air-oxidation affords the deep blue dimethyl azulene-1,2-dicarboxylic acid (Chart 3, C). Although this is not a known derivative, the spectrum is quite similar to that

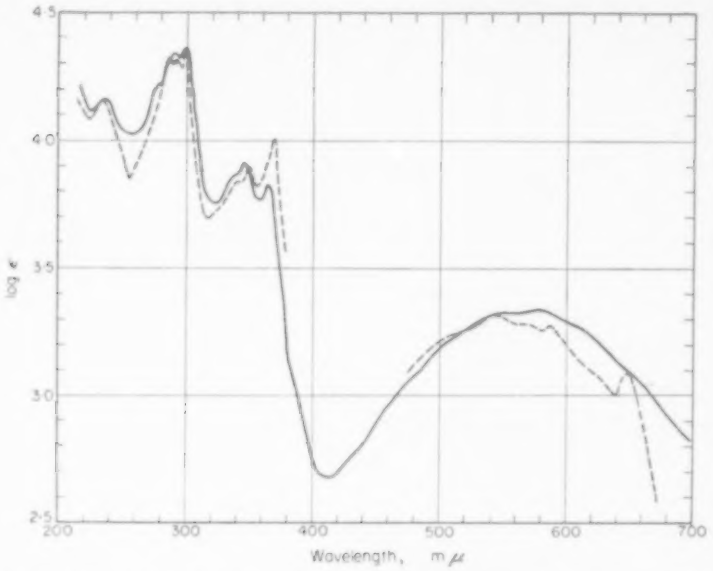


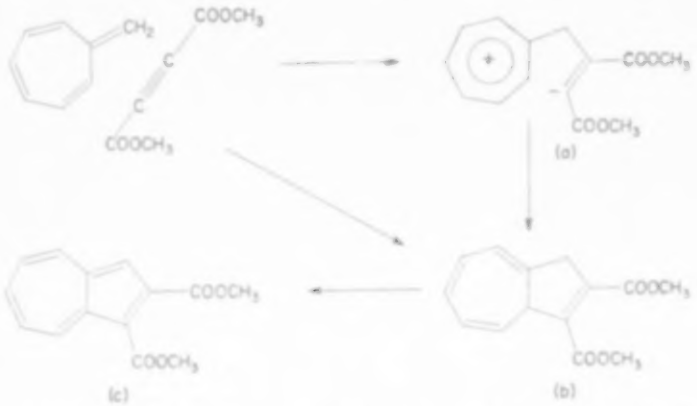
FIG. 2. Ultraviolet and visible spectra of 1-carbomethoxyazulene in cyclohexane (– – – –) and of 1, 2-dicarbomethoxyazulene (———) in isooctane.

reported by Anderson and Tazuma for methyl azulene-1-carboxylate[37] (Fig. 2). The reaction can be rationalized as the 1,3 (or 1, 8) concerted addition to heptafulvene by analogy with the Diels-Alder reaction or as a two-step ionic process (Chart 3, A) like that favored by Boekelheide for the similar reaction of pyrrocoline with dimethyl acetylene dicarboxylate.[38] The formation of a derivative of azulene, containing as it does the original structural element of methylenecycloheptatriene, constitutes further support for the structural assignment.

In the preparation of the 7-cycloheptatrienylmethyl amine by the lithium aluminum hydride reduction of 7-cycloheptatrienylcarboxamide, a dihydro derivative was obtained as its crystalline trimethyl 7-cycloheptadienyl ammonium derivative. This material, showing no absorption in the ultraviolet above 210 mμ, was transformed by Hofmann elimination into an olefin with a maximum at 284 mμ and absorption in the infrared indicative of a methylene group. Although we have made no further

[37] A. G. Anderson, Jr. and J. J. Tazuma, *J. Amer. Chem. Soc.* **75**, 4979 (1953).
[38a] V. Boekelheide, 16*th National Organic Chemistry Symposium*, American Chemical Society, Seattle, Washington, 15 June 1959, p. 32; [b] A. Galbraith, T. Small and V. Boekelheide, *J. Org. Chem.* **24**, 582 (1959).

effort to prove the structure, it has since been shown by Matteson *et al.* that 3-methylenecyclohepta-1,4-diene, a product of the pyrolysis of 5-methylenebicyclo[2.2.1] heptene, and our product are almost certainly identical.[39]



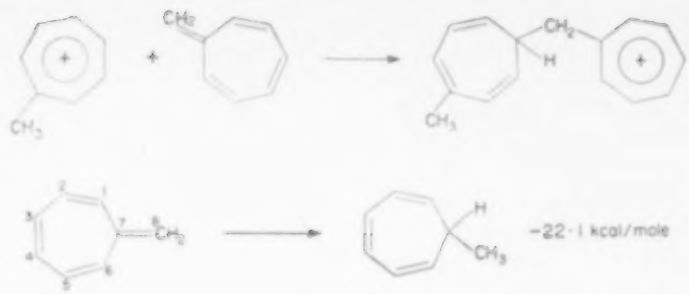
Attempts to duplicate the synthesis of methylenecycloheptatriene in the 2-cycloheptatrienyl series failed completely. Lithium aluminum hydride reduction of the corresponding carboxamide gave a very unstable amine from which no crystalline quaternary ammonium salt could be obtained.

Recently, Matteson, Drysdale and Sharkey[39] have reported the formation of methylenecycloheptatriene in the pyrolysis of 5-methylenebicyclo[2.2.1]heptene. Produced to the extent of about 0·05 per cent of theory and identified through the highly characteristic absorption spectrum, methylenecycloheptatriene was obtained in higher yield (1 per cent) by the catalytic dehydrogenation (chromia-alumina at 490°) of a mixture of 3-methylene-cycloheptadiene-1,4- and 1,5. Even at quite high temperatures, methylenecycloheptatriene is more stable in the gas phase than in the condensed. In this regard, its behavior is reminiscent of that of *p*-xylylene.[40]

One of the most characteristic properties of methylenecycloheptatriene is sensitivity to acids. Unchanged by amines and potassium hydroxide, indeed protected by their presence, heptafulvene is polymerized very rapidly by dilute acid. Shaking a pentane solution with 0·001 N aqueous hydrochloric acid leads to the instantaneous disappearance of color and precipitation of a polymer. The methylene carbon atom of methylenecycloheptatriene could be a strong Lewis base if the expected tendency to form the stable tropylium ion system[13] were not opposed by too large an aromatic resonance energy in the intact conjugated system of four double bonds. The addition of a proton might thus be expected to lead rapidly to methyltropylium ion. Methylenecycloheptatriene, having behaved as a Lewis base in the very addition of a proton, could now react at its methylene carbon with methyltropylium ion in the first step of a polymerization. There is ample analogy for the Lewis acidic properties of the tropylium ion in its varied reactions with bases to form 7-substituted cycloheptatrienes.[13] This description is quite comparable to that accepted for the

[39] D. S. Matteson, J. J. Drysdale and W. H. Sharkey, Abstracts of Papers presented at 136th Meeting of the American Chemical Society, Atlantic City, N.J., 13 September 1959, p. 30P; *J. Amer. Chem. Soc.* **82**, 2853 (1960).

[40] L. A. Errede and M. Szwarc, *Quart. Rev.* **12**, 301 (1958).



acid-catalyzed polymerization of isobutylene.[41] The marked difference in rate parallels the much easier formation of the tropylium cation.

When methylenecycloheptatriene is reacted at −70° by adding a solution in hexane rapidly to a large excess of hydrogen bromide in hexane, the polymerization is apparently avoided and a crystalline, yellow, water-soluble salt is formed instead. Although this bromide cannot be recrystallized and its structure has not been adequately determined, it is most probably methyltropylium bromide. Indeed, Dauben *et al.*[42] report that the bromide is hygroscopic and unstable and feel that the stability previously claimed by Dewar and Pettit[43] is doubtful.

Phenyllithium, like the weaker nucleophillic reagents, ammonia and hydroxide ion, does not add to heptafulvene. This behavior is in marked contrast to that of fulvene and its derivatives which do react with strong bases by addition. The calculated π-electron delocalization energies of fulvene and heptafulvene are quite close (0·50 and 0·57 α, 1·466 and 1·994 β, and 0·638 and 0·779 γ, respectively)[7] while those of the cyclopentadienide and cycloheptatrienide anions (2·48 and 2·12 β)[6] are also quite close. Disregarding questions of rate, activation energy and strain, the difference in exothermicity in the reaction with a base should be in the order of 0·89 β in favor of reaction with fulvene. Perhaps this difference represents adequate theoretical justification for the failure of heptafulvene to react. It is certainly relevant that no indication of acidity in the methylene hydrogen atoms of cycloheptatriene has been reported as yet.[44]

In respect to the carbonium ions, one has the opposite situation. Here the π-electron delocalization energies of the 5- and 7-membered cations are given as 1·14 and 3·00 β, respectively, leading to a difference of 1·33 β favoring addition of a proton to methylenecycloheptatriene. Either by this approach or by the more qualitative rule of six, the behavior towards acids and bases finds reasonable explanation.

Correlation of the theoretical and observed visible-ultraviolet absorption spectrum of heptafulvene is of interest. A self-consistent field type of calculation[23] predicts 420 mμ (2·95 eV) and 242 mμ (5·11 eV) as the position of the two transitions of lowest energies. Calculation according to the method of Pariser and Parr gives 450 mμ (2·75 eV) and 364 mμ (3·40 eV)[24] although a presumably identical type of calculation carried out by McEwen[45] gives 441 mμ (2·81 eV) and 289 mμ (4·28 eV)

[41] G. M. Burnett, *Mechanism of Polymer Reactions* pp. 407 *et seq.* Interscience, London (1959).
[42] H. J. Dauben, Jr., F. A. Gadecki, K. M. Harmon and D. L. Pearson, *J. Amer. Chem. Soc.* **79**, 4557 (1957).
[43] M. J. S. Dewar and R. Pettit, *J. Chem. Soc.* 2021 (1956).
[44] Cf. A. Streitwieser, *Tetrahedron Letters* No. 6, 23 (1960).
[45] Dr. Lenore McEwen, private communication.

as the expected positions. From the Fig. 1, three maxima centered at 426·5 mμ (23,450 cm^{-1}; 2·91 eV), 280 mμ (37,870 cm^{-1}; 4·43 eV) and 212 mμ (47,100 cm^{-1}; 5·84 eV) can be distinguished. Whether theory and experiment are in good agreement or not depends on criteria which have not been established. The fine structure shows frequency differences in the range of 1500 to 1700 cm^{-1} and is probably indicative of absorption to a vibrationally excited state. Distortion in the excited state presumably involves the bond between the rings and the methylene group.

Discussions of π-electron delocalization energy are complicated by questions of angular strain, compressional energy, non-bonded interactions, choice of model, variations in σ-bond strength and the reliability of the theoretical calculations themselves. Turner *et al.*[35] have already reported the only relevant thermodynamic datum. The heat of hydrogenation in solution is −92·6 ± ·4 kcal/mole. The reliability of the datum is discussed in that paper and due to the fleeting nature of heptafulvene itself, cannot be comparable to data relating to stable, isolable substances. It is pointed out there that the stabilization energy of heptafulvene is about 13·6 kcal/mole. In order to avoid as many doubtful corrections as possible, we would like here to call attention only to the apparent heat of hydrogenation of the exocyclic double bond—the one that completes the supposedly conjugated system in heptafulvene. This value is the difference between the heat of hydrogenation of heptafulvene (−92·6 kcal/mole) and 7-methylcycloheptatriene (unknown, but not unreasonably taken to be equal to that of cycloheptatriene itself: −70·5 ± ·4 kcal/mole[46]). The heats of hydrogenation of methylene cycloheptane,[47a] methylene cyclohexane,[47a] methylene cyclopentane[46] and 2,4-dimethyl-1-pentane[47b] are −26·3, −27·8, −26·8 and −26·7 kcal/mole, respectively. The difference in heats of formation of unstrained, non-resonating methylcycloheptatriene and methylene cycloheptatriene calculated according to Franklin's group equivalent method[48] is −26·3 kcal/mole. The stabilization energy arising from the closing of the conjugated system by the fourth double bond is at best 4–6 kcal/mole. This value may be increased a little by guesses of the extra strain in a double bond exocyclic to a planar cycloheptatriene ring.[49] However, it does not begin to compare with the discrepancy of 36·0 kcal found on completing the benzene ring by introducing the third double bond into 1,3-cyclohexadiene.

The small discrepancy of 4–6 kcal/mole could find an explanation outside of considerations of π-electron delocalization if the changes in carbon–carbon bond strength with hybridization recently proposed by Dewar and Schmeising[50] have suitable quantitative significance. The difference between the single bonds, C_1–C_7 and C_6–C_7 (sp^2–sp^2), in heptafulvene and the corresponding ones in 7-methylcycloheptatriene (sp^2–sp^3) amounts to 2 (10·5–6·0) or 9·0 kcal/mole. Another explanation appears if the cycloheptatriene discrepancy (7 kcal/mole) is magnified in methylenecycloheptatriene through a shortening of the C_1–C_6 distance.

[35] R. B. Turner, W. R. Meador and R. E. Winkler, *J. Amer. Chem. Soc.* **79**, 4116 (1957).
[47a] R. B. Turner and R. H. Garner, *J. Amer. Chem. Soc.* **80**, 1424 (1958); [47b] R. B. Turner, D. E. Nettleton, Jr. and M. Perelman, *J. Amer. Chem. Soc.* **80**, 1430 (1958).
[48] J. L. Franklin, *Ind. Engin. Chem.* **41**, 1070 (1949).
[49] The question of coplanarity in tropilidene and heptafulvene is unresolved and, until it is (tropilidene and certain derivatives are being examined), there is not much point in trying to estimate the magnitude of the angular strain energies. Although we feel that the visible-ultraviolet spectrum is consistent with a planar structure for heptafulvene, the weight of evidence is not large. The geometry of the strain-free structure is quite far from that of the planar and leaves the double bonds at rather large angles to each other.
[50] M. J. S. Dewar and H. N. Schmeising, *Tetrahedron* **5**, 166 (1959).

Irrespective of valid arguments about the reality of resonance energy and π-electron delocalization energy, there is no striking discrepancy in the heat content of the exocyclic double bond in heptafulvene and ordinary unconjugated double bonds. In comparing chemical reactions of heptafulvene and isobutylene, little attention need be directed to differences in the heat content of the starting olefins. To a first approximation, it will suffice to consider effects of the different environments on the heat content of the hypothetical transition states. Such an argument has already been made in rationalizing the remarkable sensitivity of heptafulvene to acid.

By no traditional definition, can heptafulvene be said to be aromatic. Some of its properties, sensitivity to acids, resistance to bases, absorption of light and possibly the slightly low heat of hydrogenation, find qualitative explanation in theoretical terms. But the remarkable tendency to polymerize does not. It serves as a striking example of the danger in equating theoretically calculated π-electron delocalization energy with chemical stability.

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EXPERIMENTAL[51]

Ethyl cycloheptatriene-7-carboxylate (ethyl "norcaradiene" carboxylate)

Solutions of 50 g ethyl diazoacetate in 5000 ml dry benzene are irradiated with pairs of General Electric RS sunlamps in Pyrex flasks cooled by streams of running water.[52] The evolution of nitrogen is complete and the solution has become colorless after 3–4 days. Four combined runs are worked by removing benzene by distillation, steam distilling the residue and extracting the distillate (ca. 7500 ml) with three 300-ml portions of ether. Distillation *in vacuo* gives 88 g (31%) of ethyl cycloheptatriene-7-carboxylate, b.p. 85–86°/6 mm.

Dimethyl-7-cycloheptatrienylcarbinol (*Chart* 1, B)

In view of the close similarity between our preparation and that recently published by Ganellin and Pettit[33], details will not be given here beyond noting that two recrystallizations from pentane at −27° afforded material of m.p. 55·5–56·5° (reported[33] m.p. 59–60°; Found: C, 79·8; H, 9·3; O, 11·1. Calc. for $C_{10}H_{12}O$: C, 80·0; H, 9·4; O, 10·7%).

β,β-Dimethylstyrene (*Chart* 1, C)

(a) *From dimethyl-7-cycloheptatrienylcarbinol.* When 51 mg of carbinol, m.p. 56°, was crushed in a test-tube and treated with 1 ml 50% aqueous sulfuric acid at 10°, there was an immediate, intense evolution of heat. The oil which settled out was extracted with pentane and recovered by evaporative distillation. The infrared spectrum was identical with that of an authentic sample of β,β-dimethylstyrene.

(b) *From dimethylbenzylcarbinol* (*Chart* 1, D). A sample of the carbinol was prepared in the usual way from ethyl phenylacetate and methylmagnesium iodide. This carbinol was stable to 50% aqueous sulfuric acid at room temp and lost water only when heated to 100°, and then, slowly. The two samples of β,β-dimethylstyrene had identical infrared spectra.

7-Cycloheptatrienylcarbinol (*Chart* 1, E)

Methyl cycloheptatriene-7-carboxylate was prepared by irradiation of methyl diazoacetate in benzene in the same way and on the same scale as that described above for the ethyl ester. The yield of distilled product (b.p. 68–69·5°/5 mm; n_D^{25} 1·5102) was 32% of theory. By careful fractionation of the benzene, which had been crudely distilled from the irradiation reactions, an additional 6% could be recovered.

An ethereal (200 ml) solution of 22·5 g of this ester was added dropwise under nitrogen over a

[51] Analyses by Schwarzkopf Microanalytical Laboratory, 56–19 37th Ave., Woodside 77, New York.
[52] This procedure was developed by Dr. L. H. Knox at the Hickrill Chemical Research Foundation, Katonah, N.Y., in May, 1949, and has proved itself in the ensuing years to be consistently convenient and reliable. It is similar to that published by G. O. Schenk and H. Ziegler, *Naturwissenschaften* **38**, 356 (1951); *Liebigs Ann.* **584**, 221 (1953); G. O. Schenk, *Z. Electrochem.* **55**, 505 (1951); *Angew. Chem.* **64**, 12 (1952).

2 hr period to a stirred mixture of 7·4 g lithium aluminum hydride in 200 ml ether. After 12 hr, 30 ml water was added leaving a paste and a clear ether solution which was decanted. Three 60-ml portions ether which were used to triturate the paste were united with the main ether solution. Washing with water, drying over anhydrous magnesium sulfate and distilling through a 24 cm Vigreux column gave 14·4 g (78%) 7-cycloheptatrienylcarbinol: b.p. 83·5–85·5°/3·5 mm; n_D^{25} 1·5296 (Found: C, 78·4; H, 8·4. $C_8H_{10}O$ requires: C, 78·7; H, 8·3%).

Heating a small sample of this carbinol with 3 N aqueous sulfuric acid on the steam bath, followed by extraction with pentane and distillation, afforded styrene having an infrared spectrum identical with that of an authentic sample.

A solution of 9·15 g 7-cycloheptatrienylcarbinol in 60 ml toluene was added dropwise to a stirred suspension of 3·1 g sodamide in toluene (75 ml) at 80°. After being refluxed for 1·5 hr and then cooled to 50°, the mixture was treated with 25 ml carbon disulfide and refluxed over-night. The mixture was cooled again, treated with 15 ml methyl iodide and refluxed for 4 hr. The mixture was poured into 200 ml water and extracted with 200 ml ether. The thoroughly washed ether extract was dried and distilled, finally *in vacuo* to give 11·2 g (70%) very impure methyl xanthate, b.p. 81–86°/6 mm (Found: C, 46·3; H, 6·5; S, 42·1. $C_{10}H_{12}OS_2$ requires: C, 56·6; H, 5·7; S, 30·2%), which deposited yellow crystals of dimethyl trithiocarbonate (Found: C, 26·2; H, 4·4; S, 69·0. Calc. for $C_3H_6S_3$: C, 26·1; H, 4·4; S, 69·5%) on cooling at −70°. Pyrolysis by heating slowly to 360° in a metal bath led to the distillation of a mixture. Fractionation led to the isolation of 6 drops material, b.p. 46–48°/33 mm, having the same infrared spectrum as authentic styrene. Some dimethyl trithiocarbonate was recovered as well.

Methylenecycloheptatriene (*Chart* 2, I)

A mixture of 50·4 g methyl cycloheptatriene-7-carboxylate in 160 ml conc ammonium hydroxide was shaken vigorously at room temp for 8 hr and deposited faintly yellow crystals on cooling to 2°. These were filtered, washed with ice water and twice with small amounts of pentane and dried quickly *in vacuo in the dark*. Immediate recrystallization of the crude material (32·9 g) from 3500 ml absolute ether yielded 24·1 g colorless leaflets, m.p. 145–146°. From the mother liquor, an additional 6·0 g amide, m.p. 141·5–143·0°, was obtained (total yield: 30·1 g; 66% of theory). Sensitive to air, heat and light, the amide turns dark and melts at a lower temp unless stored at −20°. Further recrystallization serves only to lower the m.p. to 140–141°, the value reported in the literature[25,33] and obtained on purification of partially decomposed material.

Use of ethyl cycloheptatriene-7-carboxylate, as previously described,[33] requires a longer time (5–8 days) and yields impure product, m.p. 127–131°, whose m.p. can be raised no higher than 140–141° and then only by several recrystallizations, attended by such losses that in our hands the yield ranged from 8–25% of theory.

7-Cycloheptatrienylmethylamine

Cycloheptatriene-7-carboxamide (30·0 g) was added over an 8 hr period to stirred, ethereal (600 ml) lithium aluminum hydride (18·5 g) at 0° under prepurified nitrogen. After 35 hr with stirring at 0°, water (75 ml) was added, separating an ether layer which was decanted and an aqueous paste which was thrice triturated with 100 ml portions of ether. The combined ether solutions were washed once with water (200 ml) and twice with saturated aqueous sodium chloride (150 ml), dried over anhydrous magnesium sulfate and concentrated to a residue, distillation of which gave 18·8 g (70·4% of theory) of the amine, b.p. 58·0–58·5°/4·2 mm; n_D^{25} 1·5405; ultraviolet absorption spectrum in 95% ethanol: λ_{min} 224 mμ (log ε 2·92), λ_{max} 253 (log ε 3·51) (Found: C, 79·5; H, 9·3; N, 11·5. $C_8H_{11}N$ requires: C, 79·3; H, 9·2; N, 11·6%).

In the usual way from phenylisocyanate, N-(7-*cycloheptatrienylmethyl*)-N′-*phenylurea* was prepared, m.p. 98–99° after recrystallization from absolute ethanol; and from phenylisothiocyanate, N-(7-*cycloheptatrienylmethyl*)-N′-*phenylthiourea*, m.p. 110–111°, from 95% ethanol (Found: C, 70·5; H, 6·5; S, 12·8. $C_{15}H_{16}N_2S$ requires: C, 70·3; H, 6·3; S, 12·5%).

Trimethyl-7-cycloheptatrienylmethylammonium iodide (*Chart* 2, C)

A mixture of 7-cycloheptatrienylmethylamine (14·6 g), powdered potassium carbonate (40 g), methyl iodide (102 g) and absolute methanol (200 ml) was shaken occasionally over a 36 hr period.

[33] E. Buchner, *Ber. Dtsch. Chem. Ges.* **29**, 106 (1896).

The solid residue, recovered by distillation, first on the steam bath, then *in vacuo*, was extracted in a Soxhlet apparatus with 300 ml chloroform for 14 hr. On being cooled, 26·9 g colorless needles, m.p. 188–190° (dec), crystallized. The concentrated mother liquor yielded an additional 5·6 g. Two recrystallizations of the combined material from absolute methanol gave 27·2 g (86% of theory) of quaternary ammonium salt as heavy needles; m.p. 194–195° (dec); ultraviolet spectrum compensated by an equimolar solution of potassium iodide both in 95% ethanol: λ_{max} 255 (log ε 3·53) (Found: C, 45·5; H, 6·2; I, 43·8; N, 4·7. $C_{11}H_{18}IN$ requires: C, 45·4; H, 6·2; I, 43·6; N, 4·8%).

Hofmann elimination. The apparatus centered about a 25 ml pear-shaped flask fitted through a ground 14/20 joint to a simple distillation head having an inlet capillary serving as a nitrogen inlet tube and an efficient vacuum boiling aid. The side arm passed into the inlet tube of the first of two simple traps, A and B, connected in series (side-arm test-tubes with concentric inlet tubes extending to within 2 cm of the bottom). The final outlet was a two-way stopcock allowing the introduction of nitrogen or the evacuation of the system.

In a typical run, 0·500 g (1·82 mmol) of the quaternary iodide was dissolved in 5 ml of distilled water (warming was necessary) and poured into a 15 ml centrifuge tube containing silver oxide, freshly prepared by treating 0·300 g (1·73 mmol) of silver nitrate in 3 ml of water with excess 2 N sodium hydroxide, centrifuging, separating by decantation and washing in similar fashion three times with distilled water. The resulting mixture was shaken and stirred for 5–10 min and centrifuged. The supernatant solution was decanted into the 25 ml pear-shaped flask along with two 2 ml washings of the precipitated silver iodide. The solution (10–15 ml) was now concentrated by distillation at 6 mm, the bulk of the water being collected in B, the second of the two traps, by cooling to −70°.

When the volume of the aqueous solution became so low that the viscosity increased noticeably, the more concentrated droplets on the side of the flask suddenly turned pale red. At this point, A, the first trap, was immersed in a dry-ice bath (it was convenient to have replaced B shortly before this time with a clean trap) and the pressure was lowered to 0·1 mm. The decomposition proceeded smoothly and could be accelerated by heating the pear-shaped flask to 35–40°. When no more liquid remained, nitrogen was admitted and about 25 ml of a suitable solvent was poured rapidly into trap A, attention being given to proper rinsing of the inside of the inlet tube. The red condensate, a mixture of water, trimethylamine and product, must be dissolved as soon as possible after it condenses and under no circumstances must it be allowed to warm to room temperature, for the red color of the product is then replaced by that of the colorless polymer. Among the solvents employed for the extraction were propane, butane, pentane, hexane, ether, tetrahydrofuran and carbon tetrachloride. In this way, dark red solutions of methylenecycloheptatriene (I) could be obtained.

Chemical and Physical Properties of Methylenecycloheptatriene

(a) *Stability.* The stability of the red solutions varied markedly with concentration, solvent and stray acidity. All attempts to concentrate solutions and isolate the product gave rise only to polymeric material. It should be mentioned that appreciable quantities of I codistilled unchanged in the attempted isolation experiments. The most determined effort involved preparing a solution in propane and removing the solvent *in vacuo* at −60°. However, just like pentane solutions evaporated at room temp on a watch glass, this procedure resulted in a tough polymeric film.

The *polymer* softened between 50–95° and became clear from 100–120°. It was partially soluble in chloroform and benzene, insoluble in methanol and paraffins, and turned yellow on standing in air. The polymer dissolves in 9 N sulfuric acid with an intense red color turning blue on diluting with water and colorless on the addition of aqueous alkali.

When a larger quantity of methylenecycloheptatriene was concentrated *in vacuo*, in addition to polymer, an oil, possibly *dimeric*, b.p. 80°/0·5 mm, could be distilled; λ_{max} 255, 263 mμ (log ε 3·68). The infrared spectrum taken in carbon tetrachloride and carbon disulfide contained the following absorption bands (in μ): 3·31 *s*trong; 3·39 s, 3·46 *m*edium, 3·51 m, 5·75 *w*eak, 5·85 *w*, 6·15 *m*, 6·20 *sh*oulder, 6·94 *s*, 7·25 *m*, 7·44 *m*, 7·53 *w*, 7·78 *w*, 8·10 *w*, 8·57 *m*, 9·20 *w*, 9·70 *w*, 9·90 *w*, 11·26 *s*, 11·78 *s*, 12·10 *m*, 12·42 *w*, 12·83 *m*, 13·05 *s*, 13·30 *s*, 13·38 *s*, 14·16 *very s*, 14·46 *s*, 14·64 *s*. The material darkened upon standing under nitrogen, and gave positive tests for unsaturation with potassium permanganate, bromine, and reacted vigorously with 9 N sulfuric acid.

Shaken with dilute aqueous acid (0·0001 N hydrochloric acid), solutions of I polymerized very fast. Consistently, solutions from which trimethylamine had been removed by washing with distilled water were far less stable than unwashed, protected solutions. For example, a washed hexane solution

of I (0·3%) had decomposed (lost its color) appreciably in 30–40 min at −60°, whereas unwashed solutions and those of much lower concentration (0·03–0·003%) were considerably more stable. An ethanol or tetrahydrofuran solution (ca. 0·1%) still containing trimethylamine was only half-decomposed after 2–4 days. I appeared to be slightly soluble and stable in liquid ammonia (from which it could be extracted with absolute ether).

(b) *Hydrogenation to methylcycloheptane.* A sample of I from 0·500 g quaternary ammonium salt in a mixture of 10 ml pentane and 10 ml methanol (both layers were intensely red) was hydrogenated at 35 lb in a Parr apparatus over platinum oxide catalyst. Worked up by pouring into water, separating, drying and distilling the pentane through a 25 cm Vigreux column at a 10 to 1 reflux ratio, the reaction yielded a small residue which was distilled in an Emich tube to give 43 mg (23%) of methylcycloheptane: b.p. 136°; d_4^{26} 0·800; n_D^{26} 1·4392.

An authentic sample was prepared from cycloheptanone and methyl magnesium iodide by dehydration of the resulting 1-methylcycloheptanol with *p*-toluenesulfonic acid and hydrogenation of the resulting olefins: b.p. 136·1°; d_4^{26} 0·798; n_D^{26} 1·4390. The infrared spectra of the two samples, taken neat in a 0·1 mm cell, were superimposable from 2–15 μ but for two very weak shoulders (amounting to about 2% difference in % transmission) present in the authentic sample. The physical constants reported for methylcycloheptane are b.p. 135–136°, d_4^{18} 0·7981; n_D^{25} 1·4388.[24]

Quantitative hydrogenation was carried out in order to determine the extinction coefficient of the visible and ultraviolet spectrum. The first method depended on the quantitative isolation of methylcycloheptane. A solution of I from 0·500 g quaternary iodide in 20 ml hexane was washed thrice with 40 ml portions water, dried for 2 min. with anhydrous magnesium sulfate and made up to 20·0 ml. A 1·00 ml aliquot was removed, diluted to 10·00 ml and used to determine the absorption spectrum. The remaining 19 ml was hydrogenated at 50 lb in a Parr apparatus with platinum oxide for 28 hr. The resulting solution was concentrated carefully, passed through an 11 × 200 mm column of activated alumina, using 30 ml pentane. The eluate was concentrated, diluted with 5 ml carbon tetrachloride and concentrated further to 0·5 ml. This residue was diluted carefully to 1·00 ml. From the density of the infrared bands at 3·49, 6·82 and 7·24 μ (the spectrum corresponded well with that of authentic methylcycloheptane), the concentration of methylcycloheptane was calculated to be 0·58 M. On the assumption that this accurately represented the amount of methylenecycloheptatriene produced (corresponding to a yield of 38% of theory) the following extinction coefficients resulted: log ε 4·082, 2·681 and 2·689 at 279, 405 and 430 mμ, respectively. Any error resulting from loss of methylcycloheptane during the isolation procedure would lie in the direction of underestimating the concentration of I. Accordingly, these are *maximum* values for the extinction coefficients.

The second method, consequent on the experimental determination of the heat of hydrogenation at Rice University, Houston,[25] depended on the quantitative measurement of hydrogen absorption to within 1%. For this work, the procedure for preparing I was varied to improve the yield and minimize polymerization. The first trap A(*v.a.*) was changed to a 50-ml, ordinary side-arm distilling flask (with the side-arm set high and connected to the second trap B with standard taper joints) with a wider (10 mm) inlet tube (leading from the pear-shaped distilling flask) to within 1 cm of the bottom. By this means, it was possible for the vapors of I to pass directly into the solvent without first condensing on the walls. In these experiments, the solvent, Diethylcarbitol (the *bis* (β-ethoxyethyl) ether of ethylene glycol; b.p. 100°/37 mm) was introduced into trap A, as usual, at the first sign of decomposition and was maintained at −15° in a salt-ice bath. The whole apparatus was shaken gently by hand to facilitate rapid dilution of the product. Following one experiment, complete evaporation of the solvent left no residue, indicating the absence of polymerization. This change in procedure also improved the *relative* yield (determined from optical density) by a factor of 1·3.

In one of several experiments, 275 ml of solution prepared from 2·000 mmol of the quaternary ammonium iodide had an optical density of 0·174 (0·173 at 0·01 mm slit; 0·175 at 0·15 mm slit) at 429 mμ in a 1 cm cell after dilution by a factor of 12·5. On catalytic hydrogenation, 6·467 mmol hydrogen was absorbed, corresponding to 81% of the theoretical yield and an extinction coefficient of 370 (log ε 2·568) in Diethylcarbitol as solvent. To the extent that any part of the hydrogen absorbed should be associated with dimer or polymer, the concentration of I would in fact have been lower than that taken. The value calculated for the extinction coefficient is therefore a *minimum* one.

(c) *Absorption spectra.* The ultraviolet and visible spectrum of I is shown in Fig. 1.

The infrared spectrum was very difficult to obtain because of the instability of solutions more

[24] G. Egloff, *Physical Constants of Hydrocarbons* Vol. II, p. 178. Reinhold (1940).

concentrated than 1%. A carbon tetrachloride solution of I was washed, dried, concentrated in a stream of nitrogen to about 1% and transferred at once to a 1 mm cell. A series of spectra were compared with that of the colorless solution remaining after 2 hr. A solution in paraffin oil was prepared by adding 0·5 ml to a pentane solution of I and concentrating. Combining the results of the two experiments gives a tentative, almost certainly incomplete spectrum: 3·25 *μ*weak, 3·32 *m*edium, 5·16 *w*, 5·45 *w*, 6·31 *s*trong, 6·48 *m*, 7·66 *w*, 8·60 *m*, 10·70 *w*, 10·86 *w*, 11·75 *s*, 12·05 *m*, 13·50 *v*ery *s*.

(d) *Ozonolysis*. A solution of 1·40 mmol ozone in methylene chloride at −70° was added to 1·38 mmol of I in 200 ml methylene chloride. As the last bit of ozone was added, the solution turned from red to yellow. Zinc powder and water were added. The methylene chloride was distilled at 40° directly into an aqueous solution of dimethyldihydroresorcinol (dimedon) buffered at pH 4. After 48 hr of occasional shaking, concentration gave a small amount of dark material which was recrystallized twice from methanol–water yielding 22 mg (6%) of the dimedon derivative of formaldehyde, m.p. 186–187°; m.p. 185–186·5° in admixture with an authentic sample. No tropone could be isolated.

(e) *Dimethyl azulene*-1,2-*dicarboxylate* (*Chart* 3, C). After 3 days at 4°, a solution of 3·43 mmol of I and 2·50 mmol dimethyl acetylene dicarboxylate in 100 ml tetrahydrofuran was concentrated on the steam bath. Benzene was added and the distillation was continued until the b.p. reached 80° and the volume was 25 ml. After the addition of 200 mg of palladium-on-charcoal (10%), a slow stream of air was passed through for 10 hr.

The mixture was filtered by passing through a short alumina column using ether as eluting solvent. The concentrated solution was chromatographed on a 13 × 50 mm alumina column with 200 ml of ether as the eluting solvent. A dark purple band separated from a dark brown, strongly adsorbed impurity. Concentration of the blue solution gave 194 mg of dark blue oil, which was chromatographed again. Middle fractions with closely similar infrared spectra were chromatographed a third time. The ultraviolet spectrum of this material is shown in Fig. 2. (Found: C, 70·3; H, 5·4; O, 24·0. $C_{14}H_{12}O_4$ requires: C, 68·9; H, 5·0; O, 26·3%.)

3-Methylenecyclohepta-1,4-diene

When the lithium aluminum hydride reduction of cycloheptatriene-7-carboxamide (*vide supra*) is carried out at room temp, exhaustive methylation of the resulting amine leads to a mixture of quaternary ammonium salts, m.p. 153–172°. Tedious fractional crystallization (aided by the appearance of two different crystalline forms—needle-like prisms and square prisms—at the fifth level which could be separated manually and used as seed) afforded trimethyl 7-cycloheptatrienylmethyl ammonium iodide, m.p. 190–191·5° (dec) and m.p. 192–193° (dec) in admixture with the sample above, and a new, light-sensitive quaternary ammonium iodide, m.p. 177–178°, apparently a trimethyl *cycloheptadienylmethyl* ammonium iodide: no maximal absorption; only end absorption: λ 204 mμ (log ε 3·42) (Found: C, 45·0; H, 7·0; I, 43·1. $C_{11}H_{20}IN$ requires: C, 45·1; H, 6·9; I, 43·3).

Subjected to the Hofmann elimination by the procedure above, but at 70–80°, this quaternary ammonium salt (0·300 g) gave a colorless liquid which was evaporatively distilled at 760 mm and 80°: λ_{max} 284, λ_{min} 236; infrared spectrum in μ: 3·24 *m*edium, 3·31 *s*trong, 3·42 *s*, 3·51 *m*, 5·60 *m*, 5·75 *m*, 5·82 *w*eak, 6·24 *m*, 6·35 *m*, 6·90 *m*, 6·98 *s*, 7·08 *m*, 7·25 *w*, 7·58 *w*, 7·65 *w*, 8·05 *m*, 8·29 *m*, 8·59 *m*, 9·85 *w*, 10·03 *w*, 10·60 *m*, 11·21 *v*ery *s*, 11·37 *s*, 11·77 *m*, 12·30 *m*, 12·70 *vs*, 13·15 *m*, 13·68 *vs*, 13·92 *m*, 15·05 *m*.

2-Cycloheptatrienylcarboxylic acid

A mixture of 35·6 g crude methyl 7-cycloheptatrienylcarboxylate and 250 ml 2 N sodium hydroxide was refluxed for 1½ hr. The homogeneous red solution was cooled, extracted twice with ether, and acidified with 2 N sulfuric acid. The acidic mixture was extracted 4 times with 60-ml portions ether. The combined ethereal extracts were dried over anhydrous magnesium sulfate and distilled on a water bath to dryness. The brown residue was sublimed to give 28·7 g of a mixture of phenylacetic acid and 2-cycloheptatrienylcarboxylic acid. Four recrystallizations of the mixture from *n*-hexane gave 12·3 g pure acid, m.p. 70–71°, and from the mother liquors, an additional 4·2 g was obtained, making the overall yield 51% of theory.

2-Cycloheptatrienylcarboxamide

A mixture of 12·6 g of the above acid and 24 g thionyl chloride was cautiously warmed on a steam bath with swirling, and refluxed for 1 hr. The excess thionyl chloride was removed *in vacuo*, and the

residue dissolved in 500 ml absolute ether. The solution was then rapidly stirred in an anhydrous ammonia atmosphere; after 1 hr, the entrance tube for the ammonia was lowered into the mixture, and the ether solution was saturated with ammonia. The precipitated ammonium chloride was filtered and washed 3 times with warm fresh ether. The combined ether filtrates were concentrated on a water bath. Sublimation of the tan residue at 90° and 0·1 mm gave 10·8 g (86% of theory) of 2-cycloheptatrienylcarboxamide as colorless crystals, m.p. 129·5–130·5°.

Attempted preparation of 2-cycloheptatrienylmethyl amine

To a stirred mixture of 6·2 g lithium aluminum hydride and 200 ml ether, at −40° under an atmosphere of dry prepurified nitrogen, 10·5 g of the powdered amide was added over a period of 6 hr. The yellow mixture was stirred for an additional 20 hr at −40 to −30°, and then allowed to warm to 0°. To the stirred mixture, 35 ml water was added dropwise keeping the temp of the reaction mixture at 0°. The dark brown ether solution was decanted from the pasty inorganic salts, which were then triturated twice with 100-ml portions of fresh ether. The combined ether solutions were dried at 0° over anhydrous magnesium sulfate for 3 hr, and then distilled under 300 mm pressure at 15°. All attempts to distill the resulting brown residue in a short path still yielded polymeric resin. Repetition of the reduction and immediate treatment of the crude ethereal solution with methyl iodide, potassium carbonate, and absolute methyl alcohol at room temp gave only a polymeric resin, from which no crystalline quaternary ammonium iodide could be obtained.

The reaction of methylenecycloheptatriene to acids

Bromine, iodine and boron trifluoride immediately polymerize heptafulvene. The same is true of aqueous hydrogen chloride and hydrogen bromide, although polymerization is slower with aqueous acetic acid or phenol. It was not possible to prepare a picrate; even at −120° only polymer and trimethylammonium picrate resulted from the reaction of ethanolic picric acid with a freshly prepared solution of heptafulvene.

The addition of a solution of heptafulvene in hexane to a solution of hydrogen bromide in hexane at −80° gave a crystalline, yellow precipitate. This material became gummy at −20° and was completely soluble in water.

The reaction of methylenecycloheptatriene to sodium

Reacting a piece of scraped sodium under a solution of methylenecycloheptatriene in tetrahydrofuran at room temperature produced a deep blue-black solution from which only intractable polymeric material could be isolated.

A solution of methylenecycloheptatriene in 20 ml of absolute ether from 0·500 g trimethyl 7-cycloheptatrienylmethyl ammonium iodide was dried over potassium hydroxide pellets at 0° for 30 min and pumped into a solution of sodium in 150 ml liquid ammonia at −60°. After 15 min stirring, the black solution was decolorized by adding methanol dropwise, diluted with additional ether, warmed to evaporate ammonia, washed twice with water, dried over magnesium sulfate, and distilled. The ether distillate had λ_{max} 252 mμ, whereas the residue yielded a couple of drops of material with λ_{max} 232 mμ and an inflection at 250 mμ.

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THE CONTRACTION OF RING A IN 5α-CHOLESTANE DERIVATIVES

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Abstract—The β-keto-ester which is obtained by Dieckmann cyclization of the dimethyl ester (I) of the dicarboxylic acid obtained by oxidative opening of ring A in 5α-cholestan-3-one and related compounds has been shown to have the structure IIa, by its degradation, via the unsaturated acid (Va), to A-nor-5β-cholestan-3-one (VI) and to the dimethyl ester (VIIb). The stereochemistry of compound IIa and of related A-substituted A-nor-5α-cholestanes is discussed. A-nor-5α-Cholestan-1-one (XVIIb) has been synthesized, starting from 5α-cholest-1-en-3-one (XIV).

THIS work was designed to investigate the possibilities of contracting six-membered rings in steroids and D-homosteroids to five-membered rings bearing a suitably disposed functional group. It was prompted by the observation by one of us, while working with Prof. G. Stork at Columbia University, that the dimethyl ester (I) gave a single β-keto-ester upon Dieckmann cyclization with potassium t-butoxide or with sodium hydride in benzene. Reduction of this keto-ester (IIa) with sodium borohydride or with lithium aluminium tri-t-butoxy hydride gave in good yield a single hydroxy-ester (IIIa). On treatment with phosphorus oxychloride in pyridine this failed to dehydrate, giving instead a chloro-ester (IV), which in turn afforded the unsaturated acid (Va) upon alkaline hydrolysis.

Alternatively the toluene *p*-sulphonyl derivative IIIc likewise gave the unsaturated ester (Vb) on treatment with potassium t-butoxide in t-butanol; it was unaffected by boiling collidine.

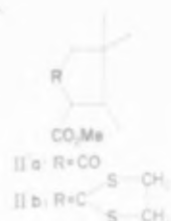
The position of the carboxyl group Va was established by Schmidt degradation. This gave a five-membered ring ketone, m.p. 79–80°; $[\alpha]_D$ +131°. Both these values are higher than those reported for A-nor-5β-cholestan-3-one.[1–3] Consequently we prepared the latter (VI) from Diels' acid as described by Windaus.[1] Careful purification of the product gave the desired pure ketone, identical with the product of degradation of compound Va.

Further confirmation of the position of the ester group in the keto-ester (IIa) and of the double bond in acid Va was given by ozonolysis of the latter compound. This gave a dicarboxylic acid (VIIa); Fischer–Speyer esterification of this gave only neutral material in the form of the dimethyl ester (VIIb), showing that neither of the carboxyl groups in the ozonolysis product is attached at the tertiary C_{10} position.

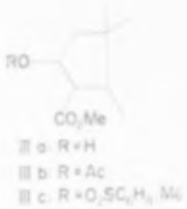
Attempted catalytic hydrogenation of the unsaturated ester (Vb) at atmospheric pressure in either ether–methanol or in ethyl acetate in the presence of palladium–carbon led to rearrangement to a different α-β-unsaturated ester, whose formulation as shown in IX is supported by the expected bathochromic shift in its ultra-violet

[1] A. Windaus, *Ber. Dtsch. Chem. Ges.* **52**, 170 (1919).
[2] D. E. Evans, A. C. de Paulet, C. W. Shoppee and F. Winternitz, *J. Chem. Soc.* 1451 (1957).
[3] B. B. Smith and H. R. Nace, *J. Amer. Chem. Soc.* **76**, 6119 (1954).

I



II a: R = CO
II b: R = C(S—CH$_2$)$_2$



III a: R = H
III b: R = Ac
III c: R = O$_2$SC$_6$H$_5$Me

IV

V a: R = H
V b: R = Me

VI

VII a: R = H
VII b: R = Me

VIII a: R = H
VIII b: R = Me

IX

X a: R = CHO
X b: R = CH$_2$OH
X c: R = CH$_2$OAc
X d: R = Me

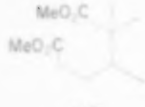
XI a, XI b

XII a: R = CH$_2$OAc
XII b: R = Me

XIII

XIV

XV a: R = R' = H
XV b: R = R' = Me
XV c: R = Me, R' = H
XV d: R' = Me, R = H



XVI

XVII a: R = CO$_2$Me
XVII b: R = H

spectrum. The saturated ester (VIIIb) was eventually obtained by desulphurization of the thioketal-ester (IIb).

The stereochemistry of these products is of interest, particularly in view of the appearance of a paper by Shoppee and Sly[4] which deals, *inter alia*, with the configuration of the two A-nor-5α-cholestan-2-ols which are obtained by reduction of A-nor-5α-cholestan-2-one, either catalytically or with sodium in ethanol or by the Meerwein–Ponndorf method.[5,6] One of these epimers, of m.p. 130°,[5] $[\alpha]_D$ +38°[4] (acetate: m.p. 80°,[4] $[\alpha]_D$ +1°[4]) gave a digitonide unlike the epimer of m.p. 155°,[5] $[\alpha]_D$ +28°[4] (acetate: m.p. 93°,[4] $[\alpha]_D$ +25°[4]), and hence these were originally designated as the β- and α-epimer respectively. Shoppee and Sly contend that Klyne's principle of enantiomeric types[7,8] cannot be used to correlate the configuration of these two epimers with those of 16β- and 16α-ols, since the latter give similar $[M]_D$ increments of the same sign. Alternatively they suggest that in view of the similar molecular rotation shown by A-nor-5α-cholestane (+90°) and 5α-cholestane (+91°) a direct correlation can be made between the above two A-nor-5α-cholestan-2-ols and between the epimeric 5α-cholestan-2-ols and their respective acetates. They come to the conclusion that the previously accepted configurations of the former pair should be reversed.

Against this, firstly, we have prepared A-nor-5α-cholestane by Wolff–Kischner reduction of A-nor-5α-cholestan-2-one, and have found the pure product to be higher in melting point and lower in specific rotation ($[M]_D$ +74°) than previously reported.[9] Secondly, it is not clear to us why, if corelation of A-nor-5α-cholestane derivatives with those of 5α-cholestane is at all valid, A-nor-5α-cholestan-2-ols should then be compared with 5α-cholestan-2-ols (and not with 5α-cholestan-3-ols, in which case incidentally Shoppee and Sly's conclusions would have to be reversed).

While it is true that $\Delta[M]_D$ values for 16β- and 16α-hydroxyl groups are not very much different, we wish to point out that those of 16β- and 16α-acetoxy groups differ considerably and consistently. From the wealth of examples now available from the literature it is clear that $\Delta[M]_D$ (16β-OAc) is either positive[8] or slightly negative,[10,11] while $\Delta[M]_D$ (16α-OAc) is always strongly negative,[8,10–12] so that $[M]_D$ (16β-OAc) — $[M]_D$ (16α-OAc) is always positive, ranging from +67°[9,13] to +410°.[14] If Klyne's theory is applicable then in nor-ring A, this being enantiomeric to ring D, $[M]_D$ (2β-OAc) — $[M]_D$ (2α-OAc) should be negative. Using Shoppee and Sly's data this is the case only if their conclusions are reversed and the heretofore accepted configurations for the two A-nor-5α-cholestan-2-ols retained (see Table 1.)

These arguments are pertinent presently when applied to the acetoxy-ester (IIIb). $[M]_D$ comparisons of methyl 3β,16α-diacetoxy-[11] and methyl 3β,16β-diacetoxy-5β-etianates[13] with methyl 3β-acetoxy-5β-etianate[11] show that here too $[M]_D$ (16β-OAc) —

[4] C. W. Shoppee and J. C. P. Sly, *J. Chem. Soc.* 345 (1959).
[5] R. E. Marker, O. Kamm, D. M. Jones and L. W. Mixon, *J. Amer. Chem. Soc.* **59**, 1363 (1937).
[6] K. Kawazaki, *Chem. Abstr.* **31**, 3060 (1937).
[7] W. Klyne, *J. Chem. Soc.* 2916 (1952).
[8] W. Klyne in Braude and Nachod, *Determination of Organic Structures by Physical Methods* p. 73. Academic Press, New York (1955).
[9] Lettre, *Z. physiol. Ch.* **221**, 73 (1933).
[10] J. Fajkos and F. Sorm, *Coll. Czech. Chem. Comm.* **21**, 1013 (1956).
[11] J. A. Moore, *Helv. Chim. Acta* **37**, 659 (1954); and refs. quoted there.
[12] V. Schwarz, V. Cerny and F. Sorm, *Coll. Czech. Chem. Comm.* **23**, 840 (1958).
[13] J. Fajkos and F. Sorm, *Coll. Czech. Chem. Comm.* **20**, 1464 (1955).
[14] D. K. Fukushima and T. F. Gallagher, *J. Amer. Chem. Soc.* **73**, 191 (1951); B. Ellis, F. Hartley, V. Petrow and D. Wedlake, *J. Chem. Soc.* 4383 (1955).

$[M]_D$ (16α-OAC) is positive (+206°) so that vicinal interference of the methoxycarbonyl group appears to be of no moment. Comparison (see Table 1) of the acetoxy-ester (IIIb) with the saturated ester (VIIIb) gives $\Delta[M]_D$ (OAc): +29° from which it can be deducted by comparison with the two 2-acetoxy-A-nor-5α-cholestanes that in IIIb the acetoxy group has the α-configuration. Since the properties of the hydroxy-ester IIIa (difficulty of ionic elimination, ease of acetylation,[15] no evidence of hydrogen bonding in its infra-red spectrum) indicate a *trans*-relationship between the two functional groups, the stereochemistry of compound IIIa must be assumed as shown, and hence that of compounds II, IV and VIII, since the reactions connecting these are such as to preclude epimerization of the methoxycarbonyl group.

TABLE 1

Compound	$[M]_D$	$\Delta[M]_D$
A-nor-5α-cholestane (present value)	+74°	
2β-acetoxy-A-nor-5α-cholestane, m.p. 80°[a]	−4	−70°
2α-acetoxy-A-nor-5α-cholestane, m.p. 93°[a]	−104	+30 } $\Delta\beta - \Delta\alpha = -100°$
3β-methoxycarbonyl-A-nor-5α-cholestane (VIIIb)	0	
2α-acetoxy-3β-methoxycarbonyl-A-nor-5α-cholestane (IIIb)	+29	Δ(2α-OAc): +29°

We now turned our attention to the possibility of contracting ring A in 5α-cholestan-3-one to give 1-substituted A-nor-5α-cholestane derivatives. It was hoped to achieve this by internal aldol cyclization of suitable dicarbonyl compounds derived from 2//3-seco-5α-cholestane, by analogy with the cyclization of 16,17-dicarbonyl-16//17-seco-D-homosteroids.[16,17] For example 2-formyl-5α-cholest-2-ene (Xa), obtained by metal hydride reduction of 2-isopropoxymethylene-5α-cholestan-3-one,[18] was converted into 2-acetoxymethyl-5α-cholest-2-ene (Xc), in which the double bond was cleaved, either by ozonolysis or by the action of lead tetra-acetate on the epimeric glycols XIa and XIb, to give a non-crystalline product which from its infra-red spectrum appeared to be the expected acetoxy-keto-aldehyde (XIIa).[19] Furthermore, 2-methyl-5α-cholest-2-ene (Xd) on ozonolysis gave what appeared to be the keto-aldehyde (XIIb). Attempted cyclization of either compounds XIIa or XIIb by a variety of methods failed to give any tangible product. Solely by passing a solution of compound XIIb through active acidic alumina a compound was isolated in low yield which may possibly be the unsaturated ketone XIII, but the amount obtained was insufficient for further characterization.

[15] H. Hirschmann and F. B. Hirschmann, *J. Amer. Chem. Soc.* **78**, 3755 (1956).
[16] J. W. Cornforth, in Cook, *Progress in Organic Chemistry* Vol. 3, p. 1. Butterworths, London (1955).
[17] W. F. Johns, *J. Amer. Chem. Soc.* **80**, 6456 (1958); G. Stork, H. N. Khastgir and A. J. Solo, *Ibid.* **80**, 6458 (1958).
[18] P. Seifert and H. Schinz, *Helv. Chem. Acta* **34**, 728 (1951); J. Fajkos and F. Sorm, *Chem. Listy* **47**, 418 (1953).
[19] The corresponding 16//17-seco-compound, A. Lardon, O. Schindler and T. Reichstein, *Helv. Chim. Acta* **40**, 666 (1957).

The failure of these reactions may be ascribed to the difficulty of carbanion formation at C_1 in these 2//3-seco compounds, presumably because of steric interference by the C_{10} angular methyl group and by ring C, and this of course would also explain the unidirectional cyclization of the diester I.[20] In the case of the 16//17-seco-D-homo-16,17-dialdehyde whose internal cyclization forms part of the total steroid synthesis by the Woodward group,[21] interference by the ring B methylene groups led, on the other hand, to preferential cyclization towards the formation of the 17-substituted steroid.[22]

TABLE 2

Compound	$[M]_D$	$\Delta[M]_D$
A-nor-5α-cholestane (present value)	+74°	
3β-methoxycarbonyl-A-nor-5α-cholestane (VIIIb)	0	(3β-CO_2Me) −74°
A-nor-5α-cholestan-2-one[9]	+525	
3β-methoxycarbonyl A-nor-5α-cholestan-2-one (IIa)	+468	(3β-CO_2Me) −57°
3β-acetoxy-5α-androstane[18]	−27	
3β-acetoxy-16β-methoxycarbonyl-5α-androstane[19]	−143	(16β-CO_2Me) −116
3β-acetoxy-16α-methoxycarbonyl-5α-androstane[19]	+17	(16α-CO_2Me) +44
A-nor-5α-cholestan-1-one (XVIIb)	+59°	
2α-methoxycarbonyl-A-nor-5α-cholestan-1-one (XVIIa)	−17	(2α-CO_2Me) −76

The unknown A-nor-5α-cholestan-1-one (XVIIb) was eventually synthesized by a method involving a C_3 carbanion. 5α-Cholest-1-en-3-one (XIV) on ozonolysis gave the dicarboxylic acid (XVa) whose monomethyl ester (XVc) was extended to the dimethyl ester (XVI). Dieckmann cyclization of the latter gave the β-keto-ester XVIIa (possible configuration of the ester group based on $[M]_D$ comparison with 3β-acetoxy-16α- and 3β-acetoxy-16β-methoxycarbonyl-5α-androstanes,[9] see Table 2), whose hydrolysis with acid gave the desired A-nor-1-ketone.

In principle it follows from the above work that a given *trans*-9-methyl-3-decalone might possibly be contractable towards either the 1- or the 3-hydrindanone, both involving the preferred 2 → 3 enolization of the former: starting either by formation of the 2-bromo-3-ketone or by oxidation of the Δ_2-enol or its equivalent.

EXPERIMENTAL

Infra-red spectra and rotations were determined in chloroform.

3β-Methoxycarbonyl-A-nor-5α-cholestan-2-one (IIa). Dimethyl 2//3-seco-5α-cholestane-2,3-dioate[23] (6·0 g, m.p. 63–64°) in dry benzene (400 ml) was refluxed with dry potassium t-butoxide (from

[20] The selective acyloin condensation of I to 3β-hydroxy-5α-cholestan-3-one, as reported by J. C. Sheehan and W. F. Erman, *J. Amer. Chem. Soc.* **79**, 6050 (1957), is probably due to a different factor.

[21] R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, *J. Amer. Chem. Soc.* **74**, 4223 (1952).

[22] A similar, though unsuccessful, approach to the contraction of ring A in allopregnanes was tried by H. Agahigian, Ph.D. Thesis, Brown Univ. (1957); *Dissertation Abstr.* **18**, 390 (1958).

[23] A. Windaus and C. Uibrig, *Ber. Dtsch. Chem. Ges.* **47**, 2384 (1914).

1 g potassium) for 14 hr, during which time small portions of solvent were distilled off. The reaction mixture was cooled and dil hydrochloric acid was added. The organic layer was washed with water, dil $KHCO_3$ solution and again with water and dried ($MgSO_4$). The solvent was removed and the residue crystallized from methanol to give needles (4·50 g) of the *β-keto-ester*, double m.p. 110–111°, 121–122°, $[\alpha]_D$ +109° (*c*, 0·69) (Found: C, 78·0; H, 10·5; O, 11·4. $C_{28}H_{46}O_3$ requires: C, 78·1; H, 10·75; O, 11·15%), bands at 5·70 μ and 5·79 μ. It gave a weak coloration with ferric chloride in methanol.[14]

Chromatography of the mother liquors gave another 1·0 g of the keto ester.

Hydrolysis by refluxing with a 3 : 1 mixture of acetic and conc hydrochloric acids gave A-nor-5α-cholestan-2-one, m.p. 105° (from methanol), $[\alpha]_D$ +143° (*c*, 1) (reported: m.p. 100–100·5°,[24] $[\alpha]_D$ +142°).[2]

*3β-Methoxycarbonyl-*A*-nor-5α-cholestan-2α-ol* (IIIa)

The above β-keto ester (3·0 g) was dissolved in tetrahydrofuran (12 ml) and methanol (12 ml) and sodium borohydride (0·4 g) was added at 0°. The solution was allowed to reach room temp during 4 hr and was then worked up in the usual manner. The crude product was chromatographed in hexane on neutral alumina (50 g). Elution with methylene chloride and then with chloroform gave the *hydroxy-ester* which crystallized from 90% methanol as felted needles, (2·0 g), m.p. 125·5–126°, $[\alpha]_D$ +14° (*c*, 1) (Found: C, 77·9; H, 11·2; O, 10·85. $C_{28}H_{48}O_3$ requires: C, 77·7; H, 11·2; O, 11·1%) sharp bands at 2·76 μ and 5·79 μ.[14]

Similar results were obtained on reduction with lithium aluminium tri-t-butoxy hydride in dry tetrahydrofuran.

Acetylation of this hydroxy ester (100 mg) in pyridine (0·8 ml) with acetic anhydride (0·2 ml) at room temp for 15 hr gave the *acetate* (IIIb), m.p. 89–90° (from methanol), $[\alpha]_D$ +29° (*c*, 1·30) (Found: C, 76·0; H, 10·4; O, 13·45. $C_{30}H_{50}O_4$ requires: C, 75·9; H, 10·6; O, 13·5%).

*2β-Chloro-3β-methoxycarbonyl-*A*-nor-5α-cholestane* (IV)

The above hydroxy ester (1·15 g) was dissolved in dry pyridine (10 ml) and phosphorus oxychloride (4 ml) was added at 0°. After standing overnight at room temp the reaction mixture was decomposed with ice and worked up in the usual manner. The crude product was chromatographed in hexane on alumina and crystallized from methanol to give the *chloro-ester* (0·9 g), needles, m.p. 125–126°, $[\alpha]_D$ −23° (*c*, 1) (Found: C, 74·1; H, 10·35; Cl, 7·85; $C_{28}H_{47}O_2Cl$ requires: C, 74·55; H, 10·5; Cl, 7·9%).

A-nor-5-cholest-2-ene-3-carboxylic acid (Va)

(a) The above chloroester (10 g) was heated under reflux for 6 hr with 20% methanolic potassium hydroxide (250 ml). Most of the methanol was removed, water was added and the resulting suspension acidified. The crude dry product (7·8 g) on crystallization from chloroform gave the *unsaturated acid*, m.p. 257–259°, $[\alpha]_D$ +78° (*c*, 0·3) (Found: C, 80·65; H, 10·8. $C_{27}H_{44}O_2$ requires: C, 80·95; H, 11·05%), λ_{max}^{EtOH} 226 mμ, ε 8000; bands at 5·98 μ and 6·25 μ.

Cautious esterification with diazomethane in ether–methanol gave the *methyl ester* (Vb), needles from methanol, m.p. 112–113°, $[\alpha]_D$ +31·5° (*c*, 1·05) (Found: C, 81·1; H, 11·0. $C_{28}H_{46}O_2$ requires: C, 81·1; H, 11·2%), λ_{max}^{EtOH} 228 mμ, ε 12000,[25] bands at 5·86 μ and 6·25 μ.

Alkaline hydrolysis returned the acid Va, identified by m.p. and mixed m.p.

(b) The hydroxy-ester (IIIa, 230 mg), dissolved in pyridine (2 ml) was treated overnight at room temp with toluene *p*-sulphonyl chloride (170 mg). To the crude dry toluene *p*-sulphonate, obtained by working up in the usual manner, a solution of potassium (87 mg) in dry t-butanol (5 ml) was added and the solution was refluxed for 2 hr. The neutral product, obtained after adding saturated sodium chloride solution and extraction with ether, was purified by chromatography and crystallization from methanol to give the above methyl ester (211 mg), m.p. 108–110°, undepressed by admixture.

Schmidt degradation of (Va). The unsaturated acid (1·5 g) was dissolved in chloroform (40 ml) and conc sulphuric acid (10 ml) was added. With stirring sodium azide (2·0 g) was added in small portions, keeping the temp below 40°; stirring was then continued for another 30 min at room temp. Water

[24] A. Windaus and O. Dalmer, *Ber. Dtsch. Chem. Ges.* **52**, 162 (1919).
[25] Cf. with methyl 3β-acetoxy-5β-androst-16-ene 17-carboxylate: λ_{max} 225 mμ, log ε 4·1; K. Meyer, *Helv. Chim. Acta* **29**, 1580 (1946).

(100 ml) was then added and the mixture heated under reflux for 4 hr. After cooling the chloroform layer was washed with water, 5% potassium hydroxide solution, again with water and dried ($MgSO_4$) and the solvent removed. The residue was chromatographed in pentane on alumina (Fisher, 25 g). Hexane eluted A-nor-5β-cholestan-3-one (VI), needles from methanol, m.p. 79–80° (corr), $[\alpha]_D$ +131° (*c*, 1·1), band at 5·77 μ. The *2,4-dinitrophenylhydrazone* had m.p. 162–164° from ethyl acetate–ethanol; reported[2] m.p. 166–167° (Found: N, 10·1, $C_{22}H_{48}O_4N_4$ requires: N, 9·75%).

This ketone, prepared from Diels' acid as described by Windaus[1], had m.p. 72–74°, $[\alpha]_D$ +105° as reported. On chromatography in pentane on active alumina this solvent eluted a small amount of non-polar material; hexane eluted the pure ketone, m.p. 77–79°, undepressed by admixture with the above product. The infra-red spectra were identical.

Ozonolysis of (Va). Excess ozonized oxygen was passed through a solution of the unsaturated acid (1·0 g) in ethyl acetate–acetic acid (1 : 1) cooled to −15°; 30% hydrogen peroxide (15 ml) was then added and the solution left at room temp overnight. It was then concentrated *in vacuo* at room temp and the residue was taken up in ether. The ether layer was washed with water, dried ($MgSO_4$) and the ether removed. The residue was triturated with pentane to give *2β/3-seco-5α-cholestane-2,4-dioic acid* (VIIa), which after crystallization from chloroform had m.p. 221–223° (Found: C, 74·05; H, 10·65; O, 15·45. $C_{26}H_{44}O_4$ requires: C, 74·25; H, 10·55; O, 15·2%).

Esterification of this dicarboxylic acid by the Fischer–Speyer method gave only neutral material which could not be induced to crystallize. A sample of this *dimethyl ester* (VIIb) was evaporatively distilled *in vacuo* (145–150°/10^{-3} mm); it had $[\alpha]_D$ +9° (*c*, 1) (Found: C, 74·9; H, 10·7; O, 14·2. $C_{28}H_{48}O_4$ requires: C, 74·95; H, 10·8; O, 14·2%), band at 5·79 μ.

3β-Methoxycarbonyl-2,2-ethylenedithio-A-nor-5α-cholestane (IIb)

The β-keto-ester (IIa, 0·30 g) was dissolved in ethanedithiol (1·5 ml) in the presence of zinc chloride (0·30 g, fused *in vacuo*) and anhydrous sodium sulphate (0·20 g). After standing overnight ether and 10% sodium hydroxide solution were added; the ether layer was washed repeatedly with water, dried ($MgSO_4$) and the solvent removed. The residue was purified by chromatography in hexane on neutral alumina and crystallization from methanol to give the *thio-ketal*, small needles, m.p. 121–122° (Found. C, 71·0; H, 9·8; S, 12·75. $C_{30}H_{50}O_2S_2$ requires: C, 71·1; H, 9·95; S, 12·65%), band at 5·80 μ:

A-nor-5α-Cholestane-3β-carboxylic acid (VIIIa)

The above thio-ketal (0·22 g) was dissolved in dioxan (5 ml) and a suspension of Raney nickel (ca. 2 g, W5) in methanol (5 ml) was added. The suspension was refluxed for 4 hr, after which it was filtered and the filtrate concentrated *in vacuo*. The residue was purified by chromatography in pentane on neutral alumina and crystallization from methanol to give the *methyl ester* (VIIIb) leaflets, m.p. 78·5–79°, $[\alpha]_D$ 0° (*c*, 1·76) (Found: C, 80·55; H, 11·4. $C_{28}H_{48}O_2$ requires: C, 80·7; H, 11·6%), band at 5·80 μ.

Alkaline hydrolysis gave the *acid*, m.p. 170° from pentane. (Found: C, 80·5; H, 11·45. $C_{27}H_{46}O_2$ requires: C, 80·55; H, 11·5%), band at 5·88 μ.

Esterification with diazomethane returned the above methyl ester, identified by m.p. and mixed m.p.

3-Methoxycarbonyl-A-nor-cholest-3-ene (XI)

The methyl ester (Vb, 150 mg) was shaken under hydrogen in either methanol–ether or in ethyl acetate in the presence of palladium–carbon (10%, 100 mg) at room temp and atm press for 5 hr. No hydrogen uptake was observed. The residue obtained after filtration and removal of the solvents was chromatographed in pentane on neutral active alumina (4 g). Hexane eluted the *unsaturated ester* (XI), long needles from methanol, m.p. 84–84·5°, $[\alpha]_D$ +66° (*c*, 1·79) (Found: C, 81·05; H, 11·2. $C_{28}H_{46}O_2$ requires: C, 81·1; H, 11·2%), λ_{max}^{EtOH} 237 mμ, ε 12000; bands at 5·90 μ and 6·09 μ.

2-Isopropoxymethylene-5α-cholestan-3-one

2-Hydroxymethylene-5α-cholestan-3-one, m.p. 180–182°, $[\alpha]_D$ +50° (*c*, 1; reported:[26] m.p. 176–178°; 6·0 g) was dissolved in dry 2-butanone (120 ml); isopropyl iodide (25 ml) and anhydrous potassium carbonate (12·0 g) were added and the suspension was refluxed with stirring for 18 hr.

[26] M. W. Goldberg and H. Kirchensteiner, *Helv. Chim. Acta* **26**, 288 (1943).

The reaction mixture was diluted with ether and water was added. The organic layer was washed 3 times with ice-cold 10% potassium hydroxide solution, then with water and dried ($MgSO_4$). The residue obtained on removal of solvents *in vacuo* (6·1 g) was used directly for the next step; a sample of the *ketone* was recrystallized from cyclohexane–isopropanol, m.p. 162–164° (Found: C, 81·4; H, 11·35. $C_{28}H_{42}O_2$ requires: C, 81·5; H, 11·5%), bands at 5·99 μ, 6·16 and 6·32 μ.

2-Formyl-5α-cholest-2-ene (Xa)

The above crude ketone (1·0 g) was dissolved in a 1 : 1 mixture of ether and methanol (20 ml) and sodium borohydride (250 mg) was added in small portions with stirring at room temp. After 3 hr most of the solvents were removed *in vacuo* at room temp, water (5 ml) was added and the mixture acidified at 0° with 10% sulphuric acid. The product was extracted with ether, the extract was washed with water, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was chromatographed in hexane on neutral active alumina (30 g). Methylene chloride–hexane (1 : 9) eluted the unsaturated aldehyde (0·35 g) which after repeated crystallization from methanol formed long needles, m.p. 130–132°, $[\alpha]_D$ +57° (*c*, 1; reported[27]: m.p. 130–132°, $[\alpha]_D$ +75°), bands at 5·95 μ, 6·06 μ.

More erratic results were obtained on reduction with lithium aluminium hydride in tetrahydrofuran.

2-Hydroxymethyl-5α-cholest-2-ene (Xb)

The above unsaturated aldehyde (650 mg) was dissolved in ether–methanol (20 ml) and sodium borohydride (300 mg) was added in small portions. After stirring for 4 hr the solvents were removed *in vacuo* at room temp and the product isolated as described for obtaining the aldehyde Xa. The crude *unsaturated alcohol* was crystallized from pentane to give needles, m.p. 140–142°, $[\alpha]_D$ +63° (*c*, 0·5) (Found: C, 83·95; H, 11·85. $C_{28}H_{48}O$ requires: C, 83·95; H, 12·1%), band at 2·76 μ.

Acetylation of this acetic anhydride–pyridine at room temp overnight gave the *acetate* (Xc), needles from methanol, m.p. 82–83° (Found: C, 81·45; H, 11·2; O, 7·3. $C_{30}H_{50}O_2$ requires: C, 81·4; H, 11·4; O, 7·25%), band at 5·79 μ.

2-Methyl-5α-cholest-2-ene (Xd)

2α-Methyl-5α-cholestan-3-one was prepared both by methylation of 2-hydroxymethylene-5α-cholestan-3-one with methyl iodide in acetone in the presence of anhydrous potassium carbonate, and by methylation of 5α-cholestan-3-one with methyl iodide via the enamine; it had m.p. 120–122·5° (reported[28]: m.p. 119–120°) undepressed on admixture with an authentic specimen.[28]

Reduction of this ketone with lithium aluminium hydride in ether gave 2α-methyl-5α-cholestan-3β-ol, m.p. 136–137° (reported[28]: m.p. 139–140°).

The latter alcohol (2·2 g) was treated in pyridine (10 ml) with toluene *p*-sulphonyl chloride (1·7 g) at room temp. The customary working-up gave the crude toluene *p*-sulphonate (m.p. 152–153°). This (3·0 g) was dissolved in dry 2,4,6-trimethylpyridine (15 ml) and the solution was refluxed under nitrogen for 2 hr. The usual working-up gave a crystalline residue which on recrystallization from ether–methanol gave long needles of the olefin (Xd, 1·55 g), m.p. 100–101°, $[\alpha]_D$ +68° (*c*, 1) (reported[29] m.p. 96°, $[\alpha]_D$ +77) (Found: C, 87·3; H, 12·55. Calc. for $C_{28}H_{48}$: C, 87·45; H, 12·55%).

Ring opening of Xc

(a) The unsaturated acetoxy compound (1·01 g) was dissolved in ethyl acetate and the solution was treated at −40° with 91 ml of a solution of ozone in the same solvent, found to contain 119 mg O_3/100 ml. The solution was allowed to reach room temp and was then stirred with 10% ferrous sulphate solution. It was then washed with water, dried ($MgSO_4$), and the solvent removed at room temp *in vacuo*, leaving a residue (1·15 g), probably XIIa which showed a band at 3·69 μ (aldehyde) and a broad carbonyl band.

(b) The unsaturated acetoxy compound (250 mg) in pure dioxan (25 ml) was added to osmium tetroxide (250 mg) in dioxan (5 ml). The resulting dark suspension of the osmate was left at room temp overnight. Hydrogen sulphide (previously passed through barium hydroxide solution) was

[27] Pl. A. Plattner and L. M. Jampolsky, *Helv. Chim. Acta* **24**, 1459 (1941).
[28] Y. Mazur and F. Sondheimer, *J. Amer. Chem. Soc.* **80**, 5220 (1958).
[29] E. Wettstein, Ph.D. Thesis, ETH, Zurich (1959).

passed through the suspension for 1/2 hr, which was then filtered through a column of celite. The filtrate was concentrated at room temp *in vacuo* and the residue crystallized from methanol, to give one *epimer* of *2-acetoxy-2ξ,3ξ-dihydroxy-5α-cholestane* (XIa, 60 mg), of m.p. 130–133° (Found: C, 75·35; H, 10·95; O, 13·5. $C_{30}H_{54}O_4$ requires: C, 75·6; H, 11·0; O, 13·4%). From the mother liquors an *epimer* (XIb) was isolated (40 mg), which after 4 recrystallizations from methanol had m.p. 166° (Found: C, 75·55; H, 11·0; O, 13·5%).

The mixture of crude XIa and XIb (245 mg) was dissolved in dry chloroform (5 ml) and anhydrous potassium carbonate (500 mg) and recrystallized lead tetra-acetate (250 mg) were added. After shaking for 1 hr a few drops of ethylene glycol were added and the suspension was filtered. The filtrate was washed with water, dried ($MgSO_4$) and the solvent removed *in vacuo*, leaving a semi-crystalline residue (XIIa, 218 mg) which showed a band at 3·69 μ and a broad band at 5·70–5·82 μ (inflections at 5·70, 5·75 and 5·81 μ).

Ring opening of (Xd). The olefin (1·5 g) was dissolved in methylene chloride (60 ml) and the solution cooled to −15°. Ozonized oxygen (5–10%) was passed in until a blue colour persisted. Acetic acid (30 ml) was added, and then zinc powder (1·5 g) in small portions with stirring during 0·5 hr. After this (negative starch-iodide reaction) the suspension was filtered, ether was added and the organic layer was washed well with water, 5% potassium carbonate solution and again with water. Drying ($MgSO_4$) and removal of solvent *in vacuo* left an oily residue (1·60 g, probably XIIb), which showed an aldehyde band at 3·69 μ and a broad carbonyl band at 5·82–5·88 μ. This yielded the *bis-2,4-dinitrophenylhydrazone* of *2-methyl-2,3-dioxo-2//3-seco-5α-cholestane*, m.p. 203–204° (decomp) from ethyl acetate–ethanol. (Found: C, 62·0; H, 7·35; N, 14·2. $C_{43}H_{56}O_8N_8$ requires: C, 61·85; H, 7·25; N, 14·4%).

Attempted internal cyclization of XIIa *and* XIIb

(a) The following conditions were tried.

On XIIa: (i) refluxing with trimethylamine benzoate in xylene for 24 hr,[19] (ii) refluxing with toluene *p*-sulphonic acid in xylene containing a small amount of acetic anhydride.

On XIIb: (iii) as for (i), (iv) refluxing with piperidine acetate in xylene for 24 hr, (v) refluxing with potassium t-butoxide in t-butanol, (vi) refluxing with aqueous potassium hydroxide at 80° under reduced pressure.[20]

Only in the case of (iii) and (iv) the crude product showed a weak band at 6·03 μ, indicating the presence of traces of α,β-unsaturated carbonyl, but no crystalline product could be isolated.

(b) The crude keto-aldehyde (XIIb, 600 mg) was transferred in hexane to a column of active acidic alumina (Woelm, activity I, 30 g). After 48 hr a yellow band was eluted with benzene–methylene chloride giving 250 mg of an oily impure product, which after a number of crystallizations from methanol gave a small amount of *1-acetyl-A-nor-5α-cholest-1-ene* (?) (XIII), m.p. 127–130° (Found: C, 83·7; H, 11·85. $C_{29}H_{48}O$ requires: C, 83·95; H, 12·1%), bands at 6·05 μ, 6·21 μ. This gave a red *2,4-dinitrophenylhydrazone*, m.p. 198–200° (decomp) (from ethyl acetate–ethanol) (Found: N, 9·65. $C_{35}H_{52}O_4N_4$ requires: N, 9·65%).

1//2-Seco-5α-cholestane-1,3-dioic acid (XVa)

5α-Cholest-1-en-3-one, (XIV), prepared by dehydrobromination of 2-bromo-5α-cholestan-3-one with lithium chloride and lithium carbonate in dimethyl formamide,[21] had m.p. 99–100°, $[\alpha]_D$ +57° (reported[22]: m.p. 98–100°, $[\alpha]_D$ +57·5°).

This (8·0 g) was dissolved in a 1 : 1 : 1 mixture of methylene chloride–ethyl acetate and acetic acid. Ozonized oxygen (5–10%) was passed at room temp through the solution until the latter became yellow (ca. 1 hr). More acetic acid and 30% hydrogen peroxide (30 ml) were then added and the mixture left overnight. The residue obtained after concentration *in vacuo* was taken up in ether; the ether layer was washed with dil acidic ferrous sulphate solution, then with water and finally with 20% potassium hydroxide solution. The acidic product was taken up in ether, the ether solution washed with water, dried ($MgSO_4$) and the ether removed. The crude residue (8·0 g) was dissolved in anhydrous methanol (200 ml) and the solution saturated with dry hydrogen chloride at 0°. After leaving the solution overnight at room temp the hydrogen chloride and methanol were removed *in vacuo* at

[20] G. I. Poos, W. F. Johns and L. H. Sarett, *J. Amer. Chem. Soc.* **77**, 1026 (1955).
[21] R. Joly, J. Warnant, G. Nominé and D. Bertin *Bull. Soc. Chim.* 366 (1958).
[22] C. Djerassi and C. R. Scholz, *J. Amer. Chem. Soc.* **69**, 2404 (1947).

room temp, the residue was taken up in ether and the ether solution extracted with several portions of 20% potassium hydroxide solution. Acidification of these extracts gave the crude monomethyl ester (XVd, 4·0 g) which was isolated with ether. A sample of this was hydrolysed by refluxing with 20% aqueous–ethanolic potassium hydroxide to give the *dicarboxylic acid*, m.p. 227–230° from ether–hexane)[23] (Found: C, 73·6; H, 10·65; O, 15·4. $C_{26}H_{44}O_4$ requires: C, 74·25; H, 10·55; O, 15·2%).

The above crude monoester (XVd, 4·0 g) was treated in ether with diazomethane. The crude neutral product obtained after the usual working-up was chromatographed in hexane on alumina (Alcoa, 150 g). Prolonged elution with hexane gave a yellow by-product (300 mg); elution with methylene chloride–hexane (1 : 4) gave the *dimethyl ester* (XVb, 2·10 g) which, crystallized from methanol, had m.p. 57–58°, $[\alpha]_D$ +29° (*c*, 10·7) (Found: C, 75·1; H, 10·65; O, 14·5. $C_{28}H_{48}O_4$ requires C, 74·95; H, 10·8; O, 14·25%), band with inflexions at 5·77 μ, 5·80 μ.

The above dimethyl ester (1·75 g) was heated under reflux with one equivalent of N sodium hydroxide (4 ml) in methanol (25 ml) for 3 hr. The solution was then concentrated *in vacuo*, water was added and the mixture extracted with hexane. The aqueous layer was acidified and the product extracted with ether. The extract was dried ($MgSO_4$) and the ether removed, giving the crude monomethyl ester, *1-methoxycarbonyl-1-1//2-seco-5α-cholestan-3-oic acid* (XVc, 1·7 g), which could not be induced to crystallize even after chromatography on silica gel, it showed neutralization equivalent: 402 (Calc. for $C_{27}H_{46}O_4$, one CO_2H: 434). The *S-benzyl thiouronium salt* had m.p. 140–141° (from nitromethane) (Found: C, 70·1; H, 9·5; S, 5·05. $C_{35}H_{56}O_4N_2S$ requires: C, 69·95; H, 9·4; S, 5·35%).

Dimethyl 1//*2-seco-5α-cholestane-1,2-dioate* (XVI)

The above monomethyl ester (XVc, 1·7 g) in dry benzene (5 ml) was treated with thionyl chloride (2 ml) and a few drops of pyridine were added. The reaction mixture was left at room temp for 0·5 hr and at 40° for 10 min. The solvents were then removed *in vacuo*, benzene being added repeatedly to remove the last traces of thionyl chloride, leaving the crude ester-acid chloride which showed bands at 5·58 μ and at 5·81 μ. This was redissolved in dry benzene (15 ml) and the filtered solution was added dropwise with stirring to an excess of diazomethane in dry ether. After 20 min at room temp the solution was concentrated *in vacuo*; the yellow residue crystallized overnight, it showed bands at 4·75 μ, 5·81 μ and 6·12 μ. This crude diazoketone was dissolved in anhydrous methanol (60 ml) and a solution (4 ml) of silver benzoate in dry triethylamine (0·5 g in 5 ml) was added dropwise with stirring during 1 hr; during this time ca. 60% of the theoretical amount of nitrogen was evolved. The reaction mixture was refluxed for 1 hr, cooled, filtered (charcoal), and the filtrate concentrated *in vacuo*. The residue was chromatographed in hexane on alumina (Alcoa, 70 g). Methylene chloride–hexane (1 : 4) eluted the *dimethyl ester* (420 mg) which had m.p. 60° (from methanol), $[\alpha]_D$ 0° (*c*, 0·4) (Found: C, 75·45; H, 10·8; O, 14·0. $C_{28}H_{48}O_4$ requires: C, 75·3; H, 10·9; O, 13·85%).

2α-Methoxycarbonyl-A-nor-5α-cholestan-1-one (XVIIa)

The above dimethyl ester (400 mg) in dry benzene (15 ml) was refluxed with dry potassium t-butoxide (from 300 mg potassium) for 12 hr, during which small portions of solvent were distilled off. The reaction mixture was treated as described for the preparation of the keto ester (IIa). The crude product (200 mg) on crystallization from methanol gave the *keto-ester*, m.p. 121·5–122·5°, $[\alpha]_D$ −4° (*c*, 0·4) (Found: C, 77·9; H, 10·95. $C_{28}H_{46}O_3$ requires: C, 78·1; H, 10·75%), bands at 5·72 μ and 5·80 μ. It gave a dark green colour with ferric chloride.

A-nor-5α-Cholestan-1-one (XVIIb)

The above keto ester (96 mg) was heated under reflux in acetic acid (5 ml) and conc hydrochloric acid (2 ml) during 1 hr, after which the mixture was concentrated to half its volume. The neutral product obtained after ether extraction was chromatographed in hexane on alumina (Alcoa, 3 g). The crystalline fractions eluted by hexane were combined and recrystallized from methanol to give needles of the *ketone* (52 mg), m.p. 84–85°, $[\alpha]_D$ +16° (*c*, 0·81) (Found: C, 83·95; H, 11·8. $C_{26}H_{44}O$ requires: C, 83·8; H, 11·9%), band at 5·80 μ, (5·78 μ in CS_2). The orange *2,4-dinitrophenylhydrazone* had m.p. 130–131° (from ethanol) (Found: C, 69·9; H, 8·95. $C_{32}H_{48}O_4N_4$ requires: C, 69·55; H, 8·75%).

[23] Ch. Tamm and R. Albrecht, *Helv. Chim. Acta* **43**, 768 (1960) report m.p. 221–222° for this compound.

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A-nor-5α-Cholestane

A-nor-5α-Cholestan-2-one (250 mg) was refluxed for 1 hr in ethylene glycol (6 ml) with 85% hydrazine hydrate (0·6 ml). To the cooled solution potassium hydroxide (0·5 g) was added and the mixture was distilled until the vapour temp reached 190°; after this reflux was continued for 3 hr. To the cooled mixture water was added and the product extracted with pentane. The washed and dried extract was concentrated and applied to basic active alumina. Pentane eluted the *hydrocarbon* which was recrystallized from ether–methanol; it had m.p. 85·5–86·0°, $[\alpha]_D$ +20·6° (*c*, 2·62) (Found: C, 87·05; H, 12·75. Calc. for $C_{26}H_{44}$: C, 87·05; H, 12·95%).

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A list of some of the papers to be published in future issues

N. L. WENDLER: D-homosteroids. Boat conformation of the D-ring.

JEFFREY A. WUNDERLICH and WILLIAM N. LIPSCOMB: The structure of 2:4 dibromomenthane.

E. HAVINGA, R. J. DE KOCK and M. P. RAPPOLDT: The photochemical interconversions of provitamin B, lumisterol, provitamin D and tachysterol.

W. KIRMSE and W. VON E. DOERING: Cyclopropanes from 1°-alkyl chlorides by α-elimination.

W. VON E. DOERING and W. KIRMSE: The absolute configuration of *trans*-1,2-dimethylcyclopropane.

A. FOFFANI, C. PECILE and S. GHERSETTI: Infra-red intensity measurements on diazo-compounds.

M. I. KABACHNIK, S. T. IOFFE, E. M. POPOV and K. V. VATSURO: *Trans*-enolization.

R. HENDERSON and R. HODGES: Ketones derived from phyllocladene.

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N. SUGIMOTO, H. WATANABE and A. IDE: The synthesis of α-amino-β-(pyrazolyl-N)-propionic acid.

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A. KALUSZYNER and S. COHEN: Cyclodehydration of diphenyltrifluoromethyl-carbinols.

N. K. KOCHETKOV, L. J. KUDRYASHOV and B. P. GOTTICH: Ketovinylation of β-dicarbonyl compounds.

D. K. BANERJEE and S. N. MAHAPATRA: Synthesis of 1,3-dimethyl-1,3-dicarboxycyclohexane-2-acetic acid—an isomer of the degradation product of abietic acid.

B. D. PEARSON: The electronic spectra of the nitronaphthylamines.

A. J. BOULTON and A. R. KATRITSKY: The tautomerism of hereroaromatic compounds with five-membered rings—I. 5-Hydroxyisoxazoles-isoxazol-5-ones.

A. J. BOULTON and A. R. KATRITSKY: The tautomerism of heteroaromatic compounds with five-membered rings—II. 3-, 4- and 5-Amino- and -acetimido-isoxazoles.

D. N. KIRK and V. PETROV: The stereochemistry of some halogenocholestan-3-ones.

B. MAJHOFER-OREŠČANIN and M. PROŠTENIK: Studies in the sphingolipids series—XVII. Synthesis and resolution of erythro and threo-C_{20}-dihydrosphingosines.

L. PICHAT, M. HERBERT et M. THIERS: Etudes sur les méthodes de préparation de la selenocystamine, selenohypotaurine et selenotaurine.

T. R. GOVINDACHARI, B. R. PAI, K. K. PURUSHOTHAMAN and S. RAJADURAI: Structure and stereochemistry of jatamansone.

N. PETRAGNANI: Aryl tellurium trihalides—II. Condensation reaction with methylketones and aromatic compounds containing electron-repelling groups.

KATSUMI KOTERA: The stereochemistry of lycorane-III (—)β-lycorane.

KATSUMI KOTERA: The stereochemistry of lycorane-III γ- and δ-lycorane.

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D-HOMOSTEROIDS

BOAT CONFORMATION OF THE D-RING[1]

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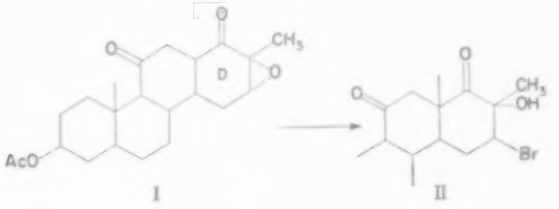
Abstract—Chemical evidence is cited in support of the boat conformation of ring-D in certain D-homosteroids. The interconversion of ketolic isomers ostensibly by methyl migration is presented.

THE observation was made several years ago that the D-homosteroid oxide (I) undergoes scission with hydrogen bromide in acetic acid to give the bromohydrin II.[2] In the latter compound the functionality, Br and OH, becomes equatorially disposed in the chair conformation of ring-D (IIa)—a consequence in contradiction to the rule of axial opening of oxides.[3] If, on the other hand, the conformation of the oxide (I) is based on a distorted boat form of ring-D (cf. Ref. 4) then the bromohydrin correspondingly will have as its immediate structural consequence the boat form IIb in conformity with the diaxial opening rule.[3] (See later discussion.)



I II

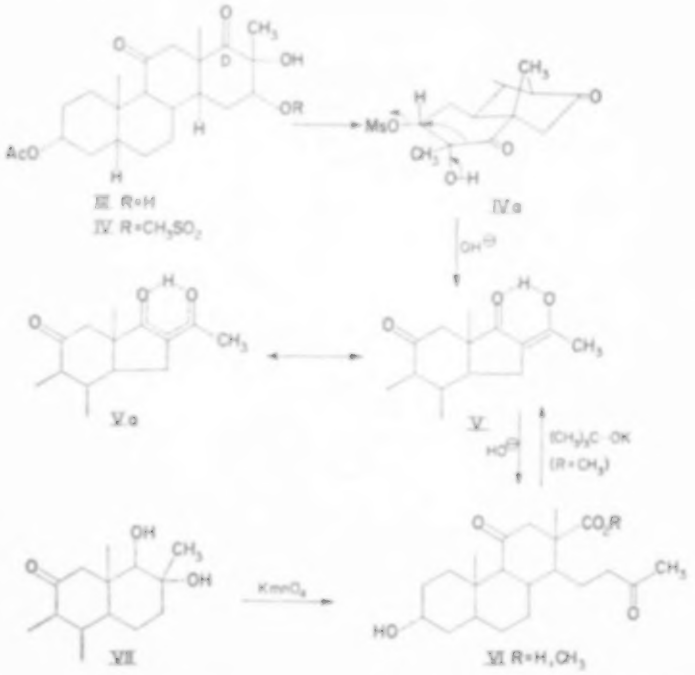
II a II b

Recently, Barton *et al.*[4] were able to isolate conformationally isomeric bromoketones in the triterpenoid field wherein one isomer was found to possess the A-ring in the boat form. A further conformational anomaly was also found in the reactions of the 2β,3β-epoxides of lanost-8-ene and lanostane. In this connection these authors made reference to the anomalous opening of the oxide (I) and suggested that this anomaly might be conformational in nature. As a result of studies in a related series

[1] For preliminary reports of this work see N. L. Wendler, *Chem. & Ind.* 1662 (1958); *Ibid.* 20 (1959).
[2a] N. L. Wendler and D. Taub, *Chem. & Ind.* 505 (1955); [b] N. L. Wendler, D. Taub, S. Dobriner and D. K. Fukushima, *J. Amer. Chem. Soc.* **78**, 5027 (1956).
[3] A. Fürst and P. L. Plattner, *Helv. Chim. Acta* **32**, 275 (1949); A. Fürst and R. Scotoni, *Ibid.* **36**, 1410 (1953).
[4] D. H. R. Barton, D. A. Lewis and J. F. McGhie, *J. Chem. Soc.* 2907 (1957).

we arrived at experimental findings which indicate the probability of the boat conformation of ring-D in certain D-homosteroids substituted at C-17.

The D-ring dihydroxyketone (III), of established structure,[5] was converted with methanesulfonyl chloride in pyridine at 0–5° to its 16-mesylate derivative (IV).[5a] The latter on warming with 5 per cent methanolic potassium hydroxide was transformed with attending ring contraction to the β-diketone (V), m.p. 170–172°, $\lambda_{max}^{CH_3OH}$ 282 mμ (ε = 8300). The infrared spectrum of V possessed bands at 5·75 μ (5-ring C=O), 5·84 μ (6-ring C=O) and at 5·99 and 6·18 μ (conj C=O). Strong hydrogen bonding in the infrared spectrum of V together with its isolation as an apparently single isomeric species, strongly suggests the geometry indicated by formula V; a completely symmetrical electron distribution structure is represented by Va. Proof of structure of the β-diketone (V) was provided by its quantitative cleavage with 20 per cent methanolic potassium hydroxide to the acid VI from which it could be re-synthesized by Dieckmann condensation of its methyl ester. The structure of the acid VI in turn was secured by comparison with an authentic specimen obtained by permanganate oxidation of the known diol VII.[6]



If the D-homo derivative (IV) possesses the chair conformation of the D-ring as in VIII then the C-17 methyl group, which is disposed *trans*-antiparallel with respect to the departing mesylate function, would be expected to migrate to give the known diosphenol (IX).[7] Since, however, ring contraction takes place instead to give the

[5a] N. L. Wendler and D. Taub, *Chem. & Ind.* 1237 (1957); [5] *J. Amer. Chem. Soc.* In press.
[6] N. L. Wendler and D. Taub, *J. Org. Chem.* **23**, 953 (1958).
[7] N. L. Wendler and D. Taub, *Chem. & Ind.* 415 (1958); N. L. Wendler, D. Taub and R. P. Graber, *Tetrahedron* **7**, 173 (1959).

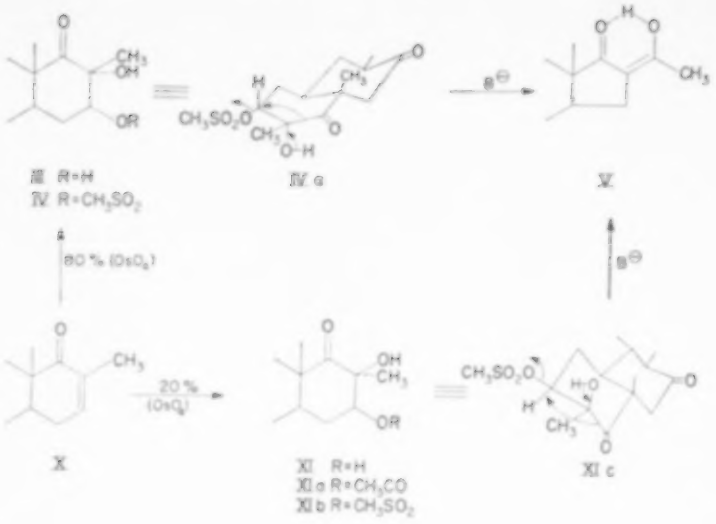
β-diketone (V), it is suggested that the D-ring possesses the boat-conformation (IVa) in order to accommodate this change in conformity with the geometrical prerequisities of *trans*-antiparallelism of the moving and departing groups. In this event the oppositional forces, arising from non-bonded interactions between the C-18 methyl group and the axial substituent at C-17 present in the chair structure could be responsible for conformational inversion.

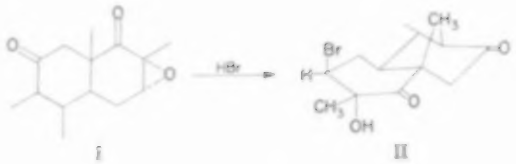
VIII IX

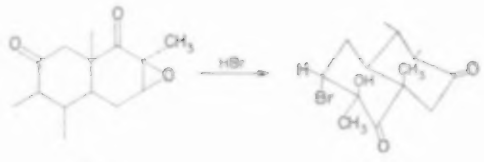
The hydroxylation of the $\Delta^{2,3}$-ketone (X) with osmium tetroxide has been described previously as giving the 16α,17α-diolone (III) as major product.[5] Chromatography of the mother liquors from the osmylation reaction revealed the presence of 20 per cent of the 16β,17β-diolone (XI). The latter as its 16-mesylate derivative XIb undergoes rearrangement with alkali to give the same β-diketone (V) as that obtained from its isomer IV. Consequently, since both isomers (IV and XIb) rearrange to the same product (V) they should have different conformations. These findings taken in consideration with the theoretical assumptions discussed above provide mutual support for the boat-conformation of the α-diolone (III) and the chair conformation of the β-diolone (XI). The foregoing is also in agreement with and, in fact, provides the interpretative basis for the directional course of opening of the α- and β-oxides I and XII.[2] The role of electronic factors *per se* in controlling the directional course of oxide scission in the case of I were considered earlier;[2b] these would now appear to be of minor significance in view of Shaw and Stevenson's demonstrated conversion of 4,5β-oxido coprostane-3-one to 4-bromo cholestenone.[8] Rather the stereo-electronic factors implicit in the diaxial opening rule would seem to be as determining here as in the established cases of simpler oxido systems. This signifies that the transition state to the formation of II from I resembles the product boat conformation. It further appears suggested that the non-bonded interaction of 1,3-axial methyl vs. methyl is greater than the corresponding 1,3-axial methyl vs. hydroxyl; further, the former in contrast to the latter appears sufficiently great by the foregoing considerations to cause conformational inversion, whereby the boat conformation provides the more stable species.

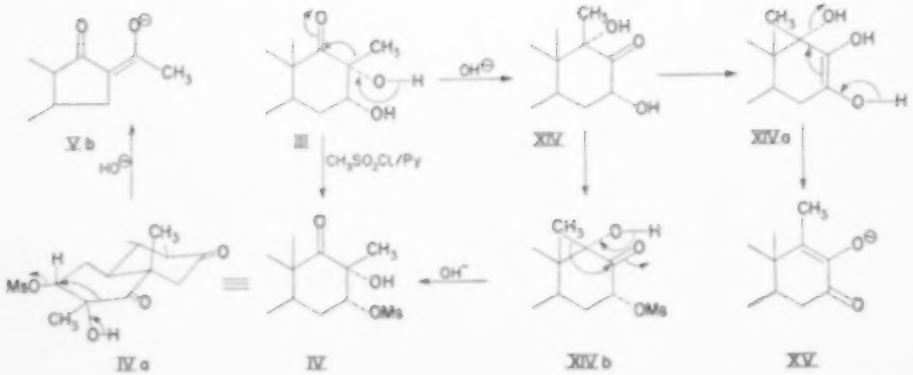
In an earlier account[5] the fate of the isomeric D-homo diolones III and XIV with alkali was discussed. The conversion of the diolone III to the diosphenol XV is considered to proceed by way of a C-17 → C-17a methyl migration to form XIV as a transitory intermediate wherein the latter can undergo β-elimination via its enediol (XIVa) to give XV. In fact, not only does the isomeric diolone XIV give the diosphenol XV on treatment with alkali but its 16-mesylate derivative (XIVb) in turn also is converted to the β-diketone (V). The latter transformation must, presumably, take

[8] J. I. Shaw and R. Stevenson, *J. Chem. Soc.* 3549 (1955). cf. Ref. 4; also W. Bergmann and M. B. Meyers, *Liebigs Ann.* 620, 46 (1959).


III R=H
IV R=CH3SO2
IV a
V
80 % (OsO4)
20 %
X
XI R=H
XI a R=CH3CO
XI b R=CH3SO2
XI c


HBr
I
II


HBr
XII
XIII


V b
III
CH3SO2Cl/Py
XIV
XIV a
IV a
IV
XIV b
XV

place by methyl migration in the sense opposite to that leading to diosphenol formation from IV, namely C-17a → C-17 to give IV as a transitory intermediate, which in turn undergoes ring contraction to the β-diketone V. The latter sequence is again uniquely defined by the structure and stereochemistry of the diolone (XIV). The apparent interconversion of the isomeric ketols via methyl migration may be considered to derive its promotional energy from the eventual collapse of each system to its respective stable enolate namely, Vb and XV.

EXPERIMENTAL

3α-Hydroxy-16-acetyl-5β-androstane-11,17-dione (V)

(a) *Alkaline rearrangement of 3α-acetoxy-16α-methanesulfonyloxy-17α-hydroxy-17β-methyl-D-homo-5β-androstane-11,17a-dione* (IV). A solution of 4 g IV[3] in 40 cc methanol was treated under nitrogen with a solution of 4 g potassium hydroxide[9] in 4 cc water and refluxed for 1 hr. The reaction mixture was cooled, acidified with 20 cc of 50% HCl aq and the methanol removed *in vacuo*. The residue was extracted with ethyl acetate and the ethyl acetate extract washed 3 times with dil $KHCO_3$ aq. Acidification of the bicarbonate extracts precipitated acid VI. The neutral ethyl acetate layer was evaporated to dryness and the residue crystallized slowly from ether to deposit the β-diketone (V) 1st crop 1 g m.p. 165–170°, recrystallization from ether m.p. 170–172° λ_{max}^{CHvOH} 282 mμ ε = 8300 $\lambda\lambda_{max}^{Chf}$ 5·75m μ (5-ring C=O), 5·84 μ (6-ring C=O), 5·99 μ and 6·18 μ (conj C=O). (Found: C, 72·83; H, 8·66. Calc. for $C_{21}H_{30}O_4$: C, 72·83; H, 8·67%).

Cleavage of the β-diketone (V) *to the acid* (VI). A solution of 500 mg β-diketone (V) in 15 cc methanol was treated with 5 g KOH in 5 cc water and refluxed in a nitrogen atmosphere for 18 hr. The reaction product was cooled, acidified with dil HCl aq and the methanol removed *in vacuo*. The residue was taken up in ethyl acetate and the ethyl acetate extracted thoroughly with $KHCO_3$ solution. Acidification of the potassium bicarbonate extract precipitated the acid VI. The latter was extracted with ethyl acetate, the solvent evaporated and the residue crystallized from ether m.p. 145–148° (cap.). This acid retained solvent of crystallization tenaciously and the latter affected the m.p. of the acid variously. For analysis a sample was pigged at 130° for 2 hr (wt. loss 5·3%). (Found: C, 69·11; H, 8·79. Calc. for $C_{21}H_{32}O_5$: C, 69·23; H, 8·79%).

The infrared spectrum of this acid was identical with an authentic sample prepared as in part B.

(b) *Preparation of* VI *by oxidative cleavage of 3α,17α,17aα-trihydroxy-17β-methyl D-homo 5β-androstane-11-one* (VII). A solution of 600 mg VII[6] in 50 cc acetone was treated with 1 g potassium permanganate and stirred for 3 hr at room temp. At the end of this period the acetone was removed in a stream of nitrogen and replaced with an equal volume of water. The reaction mixture was acidified with H_2SO_4 treated with sodium bisulfite and extracted with ether. The ether layer was washed thoroughly with $KHCO_3$ solution and the extract acidified. The precipitated acid was taken up in ethyl acetate concentrated and the residue crystallized from ether. The acid VI thus obtained was identical in m.p., mixed m.p. and infrared spectrum with the acid obtained in part A.

Resynthesis of the β-diketone (V) *from the cleavage acid* (VI). A 100 mgs ample of the acid VI was methylated in ether solution with diazomethane. The crude ester in 10 cc benzene was treated with a 1·5 cc aliquot from a solution of 1 g potassium in 30 cc t-butanol, and the reaction mixture refluxed for 2 hr. The reaction was worked up as previously described and afforded the β-diketone (V) from ether; m.p. and mixed m.p. with a sample obtained from alkaline rearrangement of IV 169–172°; the infrared spectra of the two samples were identical.

3α-Acetoxy-16β,17β-dihydroxy-17α-methyl D-homo-5β-androstane-11,17a-dione (XI)

Osmylation of the $\Delta^{\alpha\beta}$*-ketone* (X). A solution of 2 g of the $\Delta^{\alpha\beta}$-ketone (X)[3] was treated with 2·5 g osmium tetroxide in 15 cc dioxane and allowed to stand 48 hr at room temp. At the end of this period the osmate ester was decomposed with hydrogen sulfide and the reaction mixture filtered through celite. The filtrate was concentrated and chromatographed on 50 g neutral alumina employing mixtures of chloroform and ethylacetate for elution. Eluates consisting of chloroform afforded 1·1 g

[9] In practice, potassium t-butoxide (see later examples) is superior to potassium hydroxide for the rearrangement to the β-diketone (V) since the latter is not further cleaved to the acid VI with t-butoxide as it is with hydroxide.

(79%) of the known α-diolone[3] m.p. 174–176°. Eluates consisting of 10–50% ethylacetate in chloroform gave 0·3 g (21%) of the β-diolone (XI) m.p. 180–182° phase change 205–207°. (Found: C, 68·25; H, 8·28. Calc. for $C_{23}H_{34}O_6$: C, 67·98; H, 8·37%).

Acetylation of XI at room temp with acetic anhydride in pyridine gave the 3,16 *diacetate derivative* XIa m.p. 238–243° λ_{max}^{Nj} 2·84 μ (OH), 5·73 and 8·1 μ (OAc) and 5·84 μ (11 C=O). (Found: C, 66·79; H, 8·25. Calc. for $C_{27}H_{38}O_7$: C, 66·96; H, 8·04%).

Rearrangement of the β-diolone XI *as its* 16-*mesylate* (XIb) *to the β-diketone* (V). A 400 mg sample of the β-diolone XI was converted to its 16-mesylate derivative XIb with 0·25 cc methanesulfonyl chloride in 2·5 cc pyridine solution. The latter was obtained amorphous and could not be induced to crystallize, λ_{max}^{Nj} 2·8–2·9 μ (OH), 5·78 + 8·0 μ (OAc), 5·84 μ (11 C=O) and 7·3 & 8·5 μ (CH_3SO_2O).

A solution of 500 mg of the amorphous mesylate derivative XIb in 10 cc t-butanol was refluxed for 2 hr under nitrogen with potassium t-butoxide prepared from 1 g potassium metal and 20 cc t-butanol. The reaction mixture was worked up as previously described by acidification, removal of the solvent *in vacuo* and extraction of the residue into ethyl acetate. The ethyl acetate extract was washed free of all acid by $KHCO_3$ solution. Evaporation of the ethylacetate and crystallization from ether afforded the β-diketone (V), m.p. 169–172°. Mixed m.p. with authentic V not depressed. The infrared spectrum of V thus obtained was identical with previous preparations.

Rearrangement of the diolone (XIV) *as its mesylate* (XIVb) *to the β-diketone* (V). A 500 mg sample of the diolone XIV[1,3] was converted to its 16-mesylate derivative (XIVb) with 0·5 cc methanesulfonyl chloride in 5 cc pyridine. This derivative was obtained non-crystalline λ_{max}^{Nj} 2·76–2·95 μ (OH), 5·79–5·84 μ + 7·98 μ (OAc + 11 C=O), 7·31 + 8·49 μ (CH_3SO_2O).

The above mesylate derivative was refluxed for 2 hr with 30 cc 1 M potassium t-butoxide in t-butanol solution. The reaction product was worked up in the same manner described above. The product crystallized from ether m.p. 165–170°, mixed m.p. with authentic V not depressed. The infrared spectrum of this sample of V was identical with previous preparations.

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THE STRUCTURE OF 2,4-DIBROMOMENTHONE

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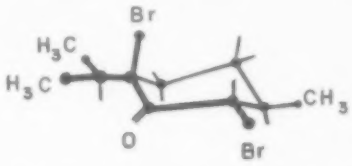
(*Received* 11 *July* 1960)

Abstract—A three-dimensional X-ray diffraction study has shown that the product obtained by bromination of D- or L-menthone is 2,4-dibromomenthone [2(a), 6(e)-dibromo-2(e)-isopropyl-5(e)methyl cyclohexanone]. The two Br atoms are *trans*, and the isopropyl and methyl groups are also *trans*. There are four molecules in the unit cell, which has symmetry $P2_12_12_1$ and dimensions $a = 13{\cdot}58$, $b = 13{\cdot}81$ and $c = 6{\cdot}25$ Å. One intermolecular Br . . . Br contact of $3{\cdot}52 \pm 0{\cdot}01$ Å occurs, a distance which is about 0·4 Å shorter than the van der Waals distance.

INTRODUCTION

BROMINATION of either D- or L-menthone in chloroform yields a corresponding dibromo derivative first thought to be[1] 1,4 dibromomenthone. Later studies[2–4] of the reactions of this dibromide led to the 2,4 positions as more probable. A recent review[5] of this evidence coupled with infrared spectra and nuclear magnetic resonance results



raised a strong possibility that the compound is 2,2-dibromomenthone. The present X-ray diffraction study of a single crystal was undertaken to resolve this problem and to establish the stereochemistry, except for the absolute configuration, of dibromomenthone.

EXPERIMENTAL

Colorless needles, obtained from ethanol solution, were covered with a thin coating of cellulosic cement in order to prevent sublimation and decomposition during X-ray exposure. Weissenberg photographs of an approximately cylindrical single crystal about 0·2 mm in diameter were taken with the use of CuKα radiation. Visual estimates of the intensities were made with the aid of a calibrated intensity scale made from single reflections from a crystal of the same compound. A superimposed powder pattern from aluminum was used as a standard for the unit cell parameters. The density of the crystals was determined by suspending them in isopropyl iodide and adjusting the temperature to $-22°$ until the last crystals just floated.[6]

There are 4 molecules of $C_{10}OH_{16}Br_2$ in an *ortho*-rhombic unit cell having dimensions $a = 13{\cdot}58 \pm 0{\cdot}03$, $b = 13{\cdot}81 \pm 0{\cdot}05$ and $c = 6{\cdot}25 \pm 0{\cdot}03$ Å. The density calculated from the X-ray measurements is 1·78 g cm^{-3}, only 0·01 g cm^3 less than the observed value. Systematic extinctions of h00 for h odd, 0k0 for k odd and 00l for l odd lead uniquely to the space group $P2_12_12_1$. Absorption corrections were made at a later stage of the investigation with $\mu = 90{\cdot}1$ cm^{-1} as the linear absorption coefficient. A total of 1204 different observed hkl reflections were measured representing 82 per cent

[1] E. Beckman and H. Eickelberg, *Ber. Dtsch. Chem. Ges.* **29**, 418 (1896).
[2] G. Cusmano, *Chem. Zentr.* **1**, 976 (1914).
[3] O. Wallach, *Liebigs Ann.* **414**, 300 (1918).
[4] P. C. Guha and B. Nath, *Chem. Ber.* **70**, 931 (1937).
[5] M. A. Morgan, M.S. Thesis, University of Minnesota (1957).
[6] J. A. Wunderlich, *Bull. Soc. Fr. Min. Crist.* **81**, 220 (1958).

of the possible total on the levels of the reciprocal lattice which were photographed. All reflections were correlated to a single scale with the aid of Weissenberg photographs of the levels hKl for $0 \leq K \leq 9$ about the *b* axis, and photographs about the *c* axis of the levels hkL for $0 \leq L \leq 4$.

Structure determination and refinement

An early attempt to solve the structure from the *c* axis projection was abandoned because of overlap of atomic positions. The three-dimensional Patterson function yielded the Br positions, which were employed to determine the phase angles of the structure factors in a three-dimensional electron density map. A clearly recognizable structure for all atoms except for hydrogens was found for 2,4-dibromomenthone in spite of diffraction ripples especially around the Br atoms.

Three-dimensional least squares refinement of the data uncorrected for absorption, and assuming isotropic thermal parameters and neglecting off-diagonal terms was unsatisfactory, leading to $R = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0{\cdot}30$ or so. A three-dimensional difference map in which isotropic Br atoms were subtracted showed that the Br vibrations were strongly anisotropic, but further least squares refinement with the use of anisotropic temperature factors for Br atoms did not appreciably lower the value of *R*. Analysis of the individual F_o's and F_c's and the behavior of the thermal parameters indicated clearly that absorption corrections were needed. The long square needles were approximated by an equivalent cylinder for these corrections, and only the hk0, hk1, hk2, and hk3 data were felt to be of sufficiently high quality for further refinement. Successive refinement by least squares methods then reached values of $R = 0{\cdot}25$ for all reflections and $R = 0{\cdot}15$ for the hk0 data. Even so, some lack of convergence, due probably to omission of off-diagonal terms, was indicated by abnormally long C_4—C_5 and C_8—C_9 bond distances; but there also seemed to be special problems associated with the inclusion of unobserved reflections, and with reflections observed at high angles of scattering.

Final refinement was carried out on the I.B.M. 704 with all off-diagonal terms, with the aid of the program of Busing and Levy[7]. Only the 958 observed hkL reflections for which $0 \leq L \leq 7$ and $\sin\theta \leq 0{\cdot}90$ were included. The final agreement factors of $r = \Sigma w(|F_o|^2 - |F_c|^2)^2/\Sigma w|F_o|^4 = 0{\cdot}168$, $R = 0{\cdot}166$ for all reflections and $R = 0{\cdot}125$ for the hk0 reflections are quite satisfactory. A summary of agreement is shown in Table 1.

The atomic parameters, shown in Table 2, have standard deviations of $\pm 0{\cdot}004$ Å for the *x*, *y*, or *z* parameters of Br, and of $\pm 0{\cdot}03$ for the *x*, *y*, or *z* parameters of C or O, as computed from the full matrix of the least squares analysis. Although the standard deviations of the isotropic temperature factors are $\pm 0{\cdot}5$ Å^2, these parameters are very likely subject to large systematic errors owing mostly to the absorption problems in this study.

Discussion of the structure

The structure is shown in Fig. 1. As might be expected if the bromination proceeds through the preferred enol form, the two Br atoms are at the 2 and 4 positions. The well known stereochemical details of methone itself are confirmed: the ring is a chair form, and the methyl and isopropyl groups are in equatorial positions. The Br at C_2 is also equatorial, but it is quite interesting that the Br at C_4 is in the axial position.

[7] W. R. Busing and H. A. Levy, Report No. 59-4-37, Oak Ridge National Laboratory (1959).

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TABLE 1. VALUES OF $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ FOR DIFFERENT CLASSES OF REFLECTIONS

	R	Range of sin θ	R	Number of reflections
All planes	0·17	0·00–0·40	0·14	112
h + k + l odd	0·17	0·40–0·50	0·14	94
h + k odd	0·17	0·50–0·60	0·17	146
k + l odd	0·17	0·60–0·65	0·16	89
h + l odd	0·17	0·65–0·70	0·17	96
h odd	0·16	0·70–0·75	0·18	100
k odd	0·17	0·75–0·80	0·19	120
l odd	0·17	0·80–0·85	0·21	111
hk0	0·12	0·85–0·90	0·18	90
0kl*	0·21			
h0l*	0·17			

* Data somewhat incomplete because only observed reflections hkL for $0 \leq L \leq 7$ and for $\sin\theta \leq 0{\cdot}90$ are included in this table.

TABLE 2. ATOMIC PARAMETERS*

Atom	x	y	z	Temperature parameters	
Br_1	0·0858	0·2655	0·5004	β_{11}	0·0040
				β_{22}	0·0016
				β_{33}	0·0211
				β_{12}	0·0006
				β_{13}	−0·0018
				β_{23}	0·0045
Br_2	−0·0510	−0·0636	0·4096	β_{11}	0·0083
				β_{22}	0·0046
				β_{33}	0·0195
				β_{12}	−0·0037
				β_{13}	−0·0004
				β_{23}	−0·0040
C_1	−0·038	0·052	0·799	B	1·0 A²
C_2	−0·007	0·051	0·565		1·3 A²
C_3	0·107	0·062	0·545		2·5 A²
C_4	0·151	0·156	0·649		0·8 A²
C_5	0·120	0·150	0·875		1·8 A²
C_6	−0·001	0·139	0·918		2·2 A²
C_7	−0·147	0·038	0·836		2·5 A²
C_8	0·254	0·155	0·628		1·7 A²
C_9	0·288	0·164	0·379		2·4 A²
C_{10}	0·307	0·239	0·754		4·1 A²
O	0·156	−0·001	0·484		4·6 A²

* x, y and z are expressed as fractions of a, b, and c respectively.

Models suggest that the H . . . H interactions may be serious if the isopropyl groups became axial, although when Br is axial there are some Br . . . H contacts which appear to be somewhat shorter than the sum of van der Waals radii. However, short intramolecular Br . . . H interactions may be less drastic than short H . . . H interactions.

We suspect that the equatorial preference of isopropyl may be lost in the enolic intermediate, and hence the resulting preference of Br for the axial position at C_4 is a question of preferred stability of the final arrangement rather than preservation of the initial stereochemistry about C_4, but we cannot be sure that another mechanism may not also be involved. The complete systematic name of this compound is thus 2(a), 6(e)-dibromo-2(e)-isopropyl-5(e)-methyl cyclohexanone.

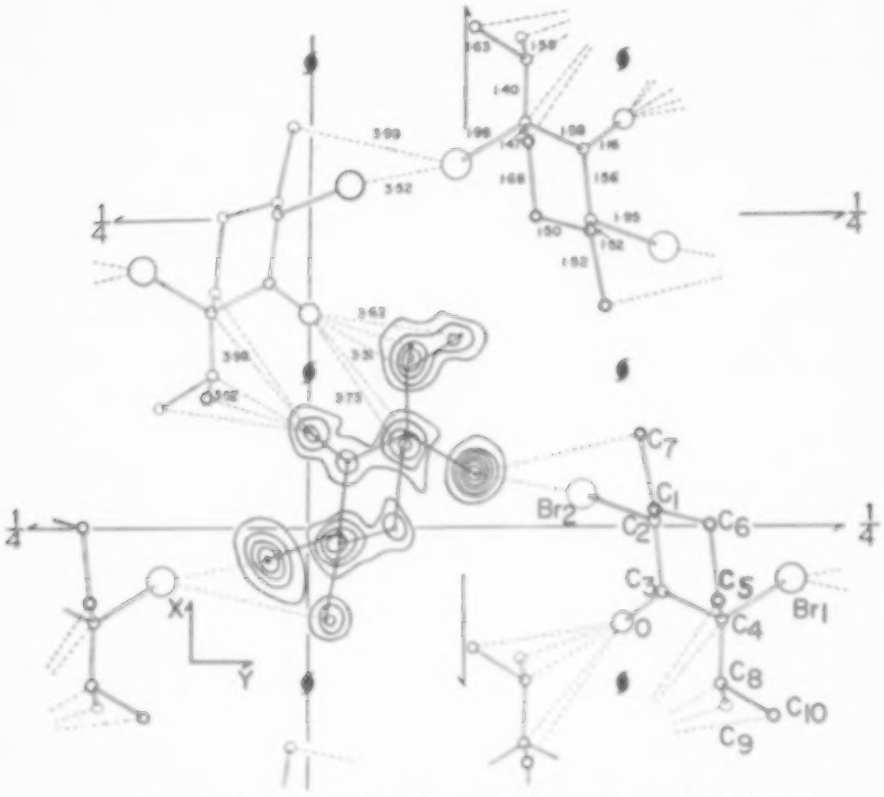

FIG. 1. The molecular arrangement in the crystal structure of 2,4 dibromomenthone. Contours are shown for the projection data (hk0) only at contour levels 0, 5, 10 . . . for C and O atoms and at levels of 0, 20, 40, . . . for Br in units of electrons/Å^2.

Bond distances and angles, shown in Table 3, have fairly high standard deviations of $\pm 0{\cdot}04$ Å for C—C, $\pm 0{\cdot}04$ for C = O, $\pm 0{\cdot}006$ Å for Br . . . Br, $\pm 0{\cdot}03$ Å for C—Br, $\pm 2{\cdot}5°$ for <C—C—C or <C—C—Br and $\pm 3{\cdot}3°$ for <C—C—O. The scatter of bond distances about the values expected upon comparison with other studies[8] is large, but within three times the standard deviations. Thus C—Br distances tend to average[8] around 1·94 Å, but distances as long as 1·99 and 2·10 Å have been found in triphenylmethyl bromide[9] and in 5′-bromo 5′-deoxythimidine,[10] respectively. Also, slightly

[8] *Tables of Interatomic Distances and Configuration in Molecules and Ions*, Special Publication No. 11 of the Chemical Society, London (1958).
[9] C. Stora, *C. R. Acad. Sci., Paris* **236**, 1661 (1953); *Bull. Soc. Chim. Fr.* **20**, 1059 (1953).
[10] M. Huber, *Acta Cryst.* **10**, 129 (1957).

short C—O distances of 1·15 Å in CCl_3CHO[11] and of 1·14 Å in halogenated *p*-quinones[12] are not unreasonable[13] and compare favorably with our value of 1·16 Å, but we cannot claim that a slight shortening is significant.

Van der Waals contacts less than 4 Å are shown in Fig. 1. The shortest C . . . O distance of 3·31 Å between C_8 and O is in reasonable agreement with an expected[13]

TABLE 3a. INTERATOMIC DISTANCES
All distances are in Å units

Br_1—C_6	1·98	C_4—C_5	1·47
Br_2—C_2	1·95	C_4—C_8	1·40
C_1—C_2	1·52	C_5—C_6	1·68
C_1—C_6	1·50	C_5—C_9	1·59
C_1—C_7	1·52	C_9—C_{10}	1·63
C_2—C_3	1·56	O—C_3	1·16
C_3—C_4	1·58		

TABLE 3b. BOND ANGLES

C_2—C_1—C_6	113°	C_5—C_4—C_8	109°
C_2—C_1—C_7	115°	C_5—C_4—Br_1	105°
C_6—C_1—C_7	111°	C_8—C_4—C_8	112°
C_1—C_2—C_3	110°	C_8—C_4—Br_1	111°
C_1—C_2—Br_2	114°	C_8—C_4—Br_1	119°
C_3—C_2—Br_2	110°	C_4—C_5—C_6	116°
C_2—C_3—C_4	115°	C_1—C_6—C_5	109°
C_2—C_3—O	122°	C_4—C_8—C_9	112°
C_4—C_3—O	122°	C_4—C_8—C_{10}	113°
C_3—C_4—C_5	104°	C_9—C_8—C_{10}	107°

contact of about 3·4 Å between CH_2 and O. The most interesting feature of the intermolecular interactions is the Br_1 . . . Br_2 distance of 3·52 ± 0·006 Å, which is approximately 0·4 Å shorter than the expected van der Waals contact[13] of 3·9 Å. Such short intermolecular halogen–halogen contacts are not uncommon in crystals, but examples in substituted organic molecules of intermediate complexity are somewhat rare. In the Br_2 crystal[14] the three contacts of 3·30, 3·30 and 3·75 Å are all less than the expected van der Waals contact. Similar shortenings have been found in Cl_2[15] and in I_2.[16,17]

The Br . . . Br contacts of 3·77 Å in the *p*-dibromobenzoate diester of iresin[18] are significantly shorter than the van der Waals contact, and are an important feature of the molecular packing in the crystal; indeed, here the thermal vibrations in the crystal are apparently comparatively high. An unusually short Br . . . Br contact of 3·32 Å in triphenylmethyl bromide[9] has been attributed to partial ionization of the C—Br bond. The 3·44 Å Cl . . . Cl contacts in 2-amino-4,6 dichloropyrimidine[19] have been attributed to hydrogen bonding, not present in our crystal. On the other hand,

[11] C. Degard, *Bull. Soc. Roy. Liège* **7**, 36 (1938).
[12] L. L. Boricelli and O. Bastiansen, *Tidsskr. Kjemi Berg.* **9**, 3 (1949).
[13] L. Pauling, *Nature of the Chemical Bond* (3rd Ed.). Cornell University Press, New York (1960).
[14] B. Vonnegut and B. E. Warren, *J. Amer. Chem. Soc.* **58**, 2459 (1936).
[15] R. L. Collin, *Acta Cryst.* **5**, 431 (1952).
[16] P. M. Harris, E. Mock, Jr. and F. C. Blake, *J. Amer. Chem. Soc.* **50**, 1583 (1928).
[17] I. I. Kitaigorodskii, V. Khotsyanova and M. Struchkov, *Zh. fiz. Khim.* **27**, 780 (1953).
[18] M. G. Rossmann and W. N. Lipscomb, *Tetrahedron* **4**, 275 (1958).
[19] C. J. B. Clews and W. Cochran, *Acta Cryst.* **1**, 4 (1948).

the short I—I distance of 3·90 Å in $P_4S_3I_2$[20], the Cl . . . Cl distance of 3·46 Å in *p*-dichlorobenzene[21] and the Br . . . Br distance of 3·76 Å in *p*-dibromobenzene[22] are further examples of distances less than the usual van der Waals contact. These comparisons are interesting and probably significant, but we feel that any detailed comparison of intermolecular contacts in organic crystals should include corrections for the crystal vibrations which are frequently a few to several tenths of an Ångstrom. In particular, we should like to be able to distinguish between the different mechanisms of shortening, such as (a) stronger binding forces in ionic and hydrogen bonded crystals as compared with molecular crystals, (b) effects associated specifically with different thermal amplitudes of crystal vibrations, rarely reliably corrected for, (c) specific charge transfer and valence interactions, probably not completely distinguishable from (a), but perhaps associated with specific electronic transitions in the complex, and, finally, (d) van der Waals contacts which are different depending upon the direction of approach and relative orientations of bonds and lone pair orbitals. The present data, though as yet insufficient, gives us some hope that these various effects can be sorted out, or that the questions can be reformulated so that these abnormal shortenings can be understood.

The C_4—Br_1 . . . Br_2 bond angle of 155·9° and the C_2—Br_2 . . . Br_1 bond angle of 161·4° are interesting aspects of this abnormally short Br_1 . . . Br_2 distance. These extraordinarily large angles are comparable to the larger of the two X—X . . . X angles of 169° and 105° which occur in solid X_2 crystals, where X is Br[14] or I.[16,17] The meaning of these angles is not clear, even as to whether increased attraction, decreased repulsion or both are occurring, but a study of the nuclear quadrupole coupling constants in the dibromomenthone crystal would be of considerable interest.

The intramolecular Br_2 . . . O distance is only 2·88 Å, considerably shorter than the expected van der Waals contact of 3·35 Å. Such shortenings are quite common, but it is most interesting that the Br_2 atom is only 0·25 Å out of the plane defined by C_2, C_4 and O atoms, in the unexpected direction that C=O just fails to be staggered relative to the two bonds from C_2 to Br_2 and H. A distortion of this order of magnitude is anticipated because of the effect of the expected near planarity of the $C_2C_3C_4O$ group. It is only remarkable that steric interactions between O and Br_2 are not more important, and that the distortion is not greater. It may well be that there are compensating attractive interactions between O and Br_2, somewhat similar to those in 1,4 dioxane-chlorine,[23] an effect which may possibly show up in a charge transfer spectrum.

It seems easiest to understand the bromination reaction as two steps in which the first Br goes into the axial position on C_4 because of the relatively poor steric situation if the isopropyl group were axial. The second Br very probably goes into the equatorial position preferentially to avoid a steric problem with Br_1, already axial.

If α-bromocyclohexanone is taken[5] as a model compound for a comparison of the H^1 resonance spectrum it is to be noted that the H atom on the α-C atom is equatorial[24] in this compound, whereas the corresponding H atom of 2,4-dibromomenthone

[20] D. A. Wright and B. R. Penfold, *Acta Cryst.* **12**, 455 (1959).
[21] J. Housty and J. Clastre, *Acta Cryst.* **10**, 695 (1957).
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is axial. A shift from about 152·5 c.p.s. (equatorial) to about 185 c.p.s. (axial) at 40 m.c. might be anticipated,[25] but it is not known whether this effect was taken into account.[5] Further substantiation of this difference between 2-bromocyclohexanone and 2,4-dibromomenthone is that the carbonyl infrared absorption is shifted[5] from about 1701 cm^{-1} in L-menthone to about 1721 cm^{-1} in 2,4 dibromomenthone, a shift suggesting approximate coplanarity of CO and CBr (equatorial). This large shift is to be compared with the relatively small shift[24] of only 4 cm^{-1} when cyclohexanone is converted to 2-bromocyclohexanone, which has an axial Br atom. Finally, with respect to the recent chemical evidence,[5] the earlier synthesis[26] of 4-bromomenthone could not be repeated, but monoiodomenthone is known.[27]

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KETONES DERIVED FROM PHYLLOCLADENE

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(*Received* 25 *July* 1960)

Abstract—Phyllocladene has been converted into some 15- and 16-oxo derivatives. The rotatory dispersion curves of these indicate that XV is the most likely structure for mirene.

SINCE the structure of phyllocladene has been established,[1] it was thought desirable to prepare a related series of compounds containing keto groups at C_{15} and C_{16} for rotatory dispersion studies. Throughout this paper a systematic nomenclature will be used, based on the parent hydrocarbon phyllocladane (I). In phylloclad-15-ene the double bond is much more hindered from the β-face, so it is probable that I corresponds to "α-dihydrophyllocladene", the sole product of catalytic hydrogenation.

Accordingly, phylloclad-15-ene was hydrated with diborane, giving an alcohol which was not characterized, but oxidized to the ketone II. It would be expected that the hydration should take place in a *cis* manner[2] from the α-face of the molecule, and hence II should have the 17-methyl group in the more congested β-configuration. This was confirmed by epimerization to the corresponding 17α-ketone (IIIa), which was also prepared by the action of boron trifluoride on 15,16-oxidophyllocladane (IVa).

In view of the nature of the Cotton effects of these ketones it was decided to prepare 15-oxo-17-norphyllocladane (IIIb). Hence, 16-oxonorphyllocladane (Va) was reduced with sodium borohydride to an alcohol which would be expected to have the structure VIa. This was converted into its tosylate which was not purified; on being heated under reflux in quinoline it underwent smooth elimination to produce the olefin VIIa. Hydrogenation of VIIa gave the parent hydrocarbon, 17-norphyllocladane (VIb).

Conversion of VIIa to the epoxide IVb followed by hydrogenolysis with lithium in ethylamine gave a mixture of alcohols which were readily separated by chromatography. That the more polar of these was the expected 16α-hydroxy-17-norphyllocladane (IXa) was shown by oxidation to Va, establishing that no skeletal rearrangements had taken place during this sequence of reactions. The other alcohol must therefore be 15α-hydroxy-17-norphyllocladane (VIIIa). Oxidation of this gave the desired ketone (IIIb).

Prior to this work other routes to IIIb were explored, but abandoned because of unsatisfactory yields. Since some of the intermediates may be of interest, these will be described.

Oxidation of phylloclad-15-ene with selenium dioxide produced an unsaturated aldehyde (VIIb) having I.R. absorption in CCl_4 at 2798, 2701 and 1679·5 cm^{-1} and U.V. absorption in MeOH at 256 mμ, ε = 10,500. This high λ_{max} is not inconsistent with the proposed structure as ketones in strained 5-membered rings are known[3] to

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[2] H. C. Brown and G. Zweifer, *J. Amer. Chem. Soc.* **81**, 247 (1959).
[3] K. Wiesner, F. Bickelhaupt, D. R. Babin and M. Götz, *Tetrahedron* **9**, 254 (1960).

absorb at high wavelengths. It should be pointed out that the ketone XI[1] is also abnormal (λ_{max} 241 mμ, ε 7800) while XII[4] absorbs at the expected wavelength (λ_{max} 230 mμ). This difference is most probably due to the strain introduced into ring D by the proximity of the methyl group at C_{10}.

The aldehyde (VIIb) was reduced to the allylic alcohol (VIIc) which could be readily oxidized back to VIIb with manganese dioxide. Epoxidation of VIIc followed by reduction with lithium in ethylamine gave a mixture of diols, one of which was isolated as its monoacetate and shown to be identical with the product (IXb) obtained from acetylation of the known[5] 16,17-dihydroxyphyllocladane. The other diol is probably 15α,17-dihydroxy-16-epiphyllocladane (VIIIb), which should be convertable to IIIb. In view of the low yield of VIIIb, this has not been attempted.

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Rearrangement of the epoxide (IVd) with boron trifluoride produced a mixture of at least three compounds, from which a substance was isolated (m.p. 108°) whose analysis would be consistent with either that of IIIc or X. However, this had I.R. absorption in CCl_4 at 1713·5 and 1747 cm^{-1} and no bands in the 2700–2800 region, which would make both these structures seem unlikely. This substance has not been further investigated.

In connexion with other work, the ketone (Vb) was prepared by alkylation of 16-oxo-norphyllocladane with propargyl chloride. The propargyl group must have an α-configuration since the β-epimer would appear, from models, to be sterically unlikely.

Rotatory dispersion curves of the five ketones, II, IIIa, IIIb, Va and Vb, were compared. The first three of these all had negative Cotton effects with only slight differences in amplitude: that of IIIa being less than II, in agreement with the assigned configurations of their 17-methyl groups. In addition Va and Vb both showed positive Cotton effects. It is clear that alkyl substitution at a carbon adjacent to a carbonyl group at C_{15} or C_{16} makes very little contribution to the Cotton effect. This confirms the observations of Bourn and Klyne[6] that the sign of the Cotton effect of ketones in rigid 5 membered rings is largely determined by the asymmetry of the ring containing the carbonyl group and that the substituents have only minor effects. Thus the structure XIII which has been proposed[7] for oxo-normirene would be anomalous if it showed a Cotton effect of different sign from that of Va. Since oxonormirene does in fact have a negative effect, we would suggest that it does not have the proposed structure.

Any formula for mirene must contain a methylene group, exocyclic to a 5 membered ring and must account the nature of the rotatory dispersion curve of its derived norketone and for its acid catalysed rearrangement to phylloclad-15-ene. It was thought possible that XIV might be capable of rearrangement to phylloclad-15-ene, the driving force being the high degree of steric interaction between the substituents at C_{10} and C_{15}. However, the ketone (IIIb), while having a rotatory dispersion curve of the same type, is not identical with oxonormirene.

The structure XV should satisfy the first two requirements for mirene, although an unusual path must be invoked for its rearrangement to phylloclad-15-ene. Work aimed at preparing structures of this type is now in progress.

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[5] C. W. Brandt, *N.Z. J. Sci. Technol.* **34B**, 46 (1952).
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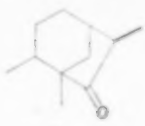
I



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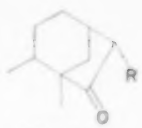
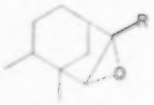
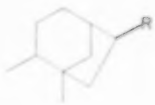


III a, R = Me
b, R = H
c, R = CH_2OAc



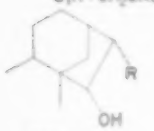
IV a, R = Me
b, R = H
c, R = CH_2OH
d, R = CH_2OAc

V a, R = H
b, R = CH_2–C≡CH



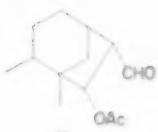
VI a, R = OH
b, R = H

VII a, R = H
b, R = CHO
c, R = CH_2OH
d, R = CH_2OAc

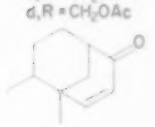


VIII a, R = H
b, R = CH_2OH

IX a, R = H
b, R = CH_2OAc



X



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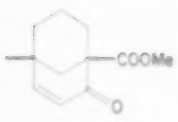

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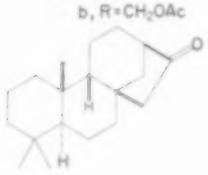
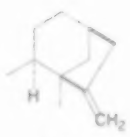
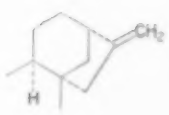


XIII



XIV



XV

EXPERIMENTAL

Rotations were measured in chloroform at 20°. M.p.'s were taken on a Kofler block and are corrected. Alumina used for chromatography had activity II. Light petroleum refers to the fraction b.p. 60–80°.

15-Oxophyllocladane (II). Lithium aluminium hydride (610 mg) in ether (25 ml) was added slowly to a solution of phylloclad-15-ene (415 mg) and boron trifluoride etherate (3·5 g) in ether (100 ml) under nitrogen. After 1 hr the product was isolated, dissolved in tetrahydrofuran (20 ml) and treated with hydrogen peroxide (5 ml, 30%) and methanolic sodium hydroxide. After a further hour the product was adsorbed from benzene on alumina and eluted with benzene ether (1 : 1) as a colourless gum which could not be crystallized. Oxidation of this material, in acetone with chromic acid/sulphuric acid gave *15-oxophyllocladane* (125 mg) as plates from methanol, m.p. 101–102°, $[\alpha]_D$ −62° (*c*, 0·8). (Found: C, 82·95; H, 11·2. $C_{20}H_{32}O$ requires: C, 83·25; H, 11·2%.)

15-Oxo-16-epiphyllocladane. II (30 mg) was heated under reflux with methanolic sodium hydroxide (5 ml, 2%) for 8 hr. Repeated crystallization of the product from aqueous methanol yielded *15-oxo-16-epiphyllocladane* (IIIa), m.p. 127·5–129°, $[\alpha]_D$ −50° (*c*, 0·5). (Found: C, 83·4; H, 11·35. $C_{20}H_{32}O$ requires: C, 83·25; H, 11·2%.)

15,16-Oxidophyllocladane (IVa). Phylloclad-15-ene (620 mg) was reacted with an excess of monoperphthalic acid in ether for 15 hr at 0°. Crystallization from methanol gave the epoxide (490 mg), m.p. 92–93°, $[\alpha]_D$ +30° (*c*, 0·9). (Found: C, 82·95; H, 10·9. $C_{20}H_{32}O$ requires: C, 83·25; H, 11·2%.)

Treatment of IVa (450 mg) in benzene (30 ml) with boron trifluoride etherate (0·5 ml) for 15 min at 20° gave a mixture of ketones (440 mg, m.p. 112–118°) which after repeated crystallization from methanol yielded 15-oxo-16-epiphyllocladane.

16β-*Hydroxy*-17-*norphyllocladane* (VIa). 16-Oxonorphyllocladane (V) (1·20 g) was treated with sodium borohydride (400 mg) in aqueous methanol (50 ml, 90%) for 12 hr at 20°. The product crystallized as needles (1·11 mg) of VIa from light petroleum, m.p. 150–151·5°, $[\alpha]_D$ +17° (*c*, 0·9). (Found: C, 82·45; H, 11·85. $C_{19}H_{32}O$ requires: C, 82·55; H, 11·65%.)

17-*Norphyllocl*ad-15-*ene* (VIIa). VIa (1·10 mg) was reacted with *p*-toluenesulphonyl chloride (1 g) in pyridine (15 ml) for 8 hr at 20°. The resulting tosylate was heated under reflux in quinoline (5 ml) and the product, in light petroleum was filtered through alumina. Crystallization from aqueous ethanol gave VIIa (940 mg) as plates, m.p. 72·5–73°, $[\alpha]_D$ +7° (*c*, 0·7). (Found: C, 88·1; H, 11·65. $C_{19}H_{30}$ requires: C, 88·3; H, 11·7%.)

17-*Norphyllocladane* (VIb). Hydrogenation of VIIa in ethyl acetate using Adams' catalyst gave VIb as plates from aqueous ethanol, m.p. 85–86°, $[\alpha]_D$ +3° (*c*, 0·9). (Found: C, 87·4; H, 12·4. $C_{19}H_{32}$ requires: C, 87·6; H, 12·4%.)

15α,16-*Oxido*-17-*norphyllocladane* (IVb). VIIa (830 mg) was allowed to react with an excess of monoperphthalic acid in ether for 24 hr at 0°. Crystallization from methanol gave IVb as plates (580 mg), m.p. 84·5–86°, $[\alpha]_D$ +16° (*c*, 0·9). (Found: C, 83·15; H, 10·65. $C_{19}H_{30}O$ requires: C, 83·15; H, 11·0%).

Reduction of the epoxide (IVb). IVb (550 mg) in ethylamine (30 ml) was treated with lithium and allowed to react for 1 hr after a permanent blue colour had appeared. The product was adsorbed on alumina from light petroleum and eluted with benzene–ether (4 : 1) as needles (180 mg from aqueous methanol) of 15α-*hydroxy*-17-*norphyllocladane* (VIIIa), m.p. 125–126° (with melting and resolidification at 116–118°), $[\alpha]_D$ +4° (*c*, 0·8). (Found: C, 82·8; H, 11·85. $C_{19}H_{32}O$ requires: C, 82·55; H, 11·65%.)

Further elution with ether gave 16α-*hydroxy*-17-*norphyllocladane* (IXa) as needles (190 mg from light petroleum), m.p. 156–157°, $[\alpha]_D$ −7° (*c*, 0·8). (Found: C, 82·9; H, 11·95. $C_{19}H_{32}O$ requires: C, 82·55; H, 11·65%.)

15-*Oxo*-17-*norphyllocladane* (IIIb). Oxidation of VIIIa (47 mg) in acetone (5 ml) with chromic acid/sulphuric acid gave the ketone IIIb as needles (39 mg from light petroleum), m.p. 132–133°, $[\alpha]_D$ −33° (*c*, 1·0). (Found: C, 82·95; H, 10·8. $C_{19}H_{30}O$ requires: C, 83·15; H, 11·0%.)

Oxidation of IXa yielded 16-oxonorphyllocladane identical with an authentic sample, $[\alpha]_D$ +71° (*c*, 0·8).

17-*Oxophyllocl*ad-15-*ene* (VIIb). Phylloclad-15-ene (1·69 g) and selenium dioxide (1·5 g) were heated together under reflux in acetic acid (20 ml) for 30 min. The product was adsorbed from light petroleum on alumina deactivated with 5% of 10% acetic acid and eluted with benzene as needles (1·49 g from light petroleum) of VIIb, m.p. 129–130°, $[\alpha]_D$ −71° (*c*, 1·0). (Found: C, 83·45; H, 10·55. $C_{20}H_{30}O$ requires: C, 83·85; H, 10·55%.)

17-*Hydroxyphyllocl*ad-15-*ene* (VIIc). Reduction of VIIb (1·30 g) with lithium aluminium hydride in ether produced VIIc as needles (1·21 g from light petroleum), m.p. 125·5–126·5, $[\alpha]_D$ +14° (*c*, 0·9). (Found: C, 83·15; H, 11·1. $C_{20}H_{32}O$ requires: C, 83·25; H, 11·2%.) This alcohol was quantitatively oxidized back to the aldehyde (VIIb) by shaking for 12 hr with manganese dioxide in chloroform.

Acetylation of VIIc by heating under reflux with acetic anhydride and sodium acetate gave 17-*acetoxyphyllocl*ad-15-*ene* (VIId) as plates from aqueous methanol, m.p. 38–39°. (Found: C, 80·15, H, 10·65. $C_{22}H_{34}O_2$ requires: C, 79·95; H, 10·35%.)

17-*Hydroxy*-15,16-*oxidophyllocladane* (IVc). Reaction of VIIc (350 mg) with an excess of monoperphthalic acid in ether for 2 days at 0° produced the epoxide as needles (270 mg from light petroleum), m.p. 149–151°, $[\alpha]_D$ +39° (*c*, 0·6). (Found: C, 78·95; H, 10·5. $C_{20}H_{32}O_2$ requires: C, 78·9; H, 10·6%.)

Similarly 17-*acetoxy*-15,16-*oxidophyllocladane* (IVd) formed needles from aqueous methanol, m.p. 86·5–87·5°, $[\alpha]_D$ +29° (*c*, 0·7). (Found: C, 76·0; H, 10·15%. $C_{22}H_{34}O_3$ requires: C, 76·25; H, 9·9%.)

Reduction of the epoxide (IVc). IVc (170 mg) was reacted with lithium in ethylamine as before. The product was acetylated with acetic anhydride in pyridine for 12 hr at 20°. Adsorption from light petroleum on alumina deactivated with 5% of 10% acetic acid, followed by elution with light petroleum gave a crude diacetate which was not obtained crystalline. Further elution with benzene–chloroform (3 : 2) gave 17-acetoxy-16-hydroxyphyllocladane (IXb; 43 mg from light petroleum), m.p. 142–143·5°. (Found: C, 76·0; H, 10·5. $C_{22}H_{36}O_3$ requires: C, 75·8; H, 10·4%.) This was identical with a specimen prepared by partial acetylation of 16,17-dihydroxyphyllocladane.

The crude diacetate from above was hydrolysed with methanolic sodium hydroxide, adsorbed from benzene on alumina and eluted with ether–methanol (19 : 1) as needles (65 mg from light petroleum–chloroform) of 15α,17-*dihydroxy*-16-*epiphyllocladane* (VIIIb) m.p. 192–193°, $[\alpha]_D$ +10° (*c*, 0·9). (Found: C, 78·75; H, 10·2. $C_{20}H_{34}O_2$ requires C, 78·4; H. 10·2%.)

Reaction of BF_3 on IVd. IVd (75 mg) in benzene was allowed to react with boron trifluoride etherate (0·2 ml) for 2 days at 0°. The product was adsorbed on deactivated alumina and eluted with benzene as needles (15 mg from aqueous methanol), m.p. 108–109·5°, $[\alpha]_D$ −2° (*c*, 0·7). (Found: C, 76·0; H, 10·15. $C_{22}H_{34}O_2$ requires: C, 76·25; H, 9·9%.)

Further elution with chloroform gave an inseparable mixture of dihydroxyacetates (43 mg) crystallizing as plates from light petroleum–chloroform, m.p. 173–179°. (Found: C, 72·35; H, 10·35. $C_{22}H_{36}O_4$ requires: C, 72·5; H, 9·95%.)

16-*Oxo*-15α-*propargylnorphyllocladane* (Vb). 16-*Oxonorphyllocladane* (520 mg) and sodamide (250 mg) in xylene (50 ml) were heated together under reflux for 4 hr. After cooling, propargyl chloride (0·5 ml) was added and the mixture heated for a further 3 hr. The product was adsorbed from light petroleum on alumina and eluted with benzene as prisms of Vb (80 mg from methanol), m.p. 168–170°, $[\alpha]_D$ +66° (*c*, 0·5). (Found: C, 84·6; H, 10·15. $C_{23}H_{32}O$ requires: C, 84·55; H, 10·3%.)

Acknowledgements—We wish to thank Professors W. Klyne and C. Djerassi for invaluable discussions and for the rotatory dispersion measurements, and Professor R. A. Raphael for his continued encouragement.

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THE SYNTHESIS OF L-α-AMINO-β-(PYRAZOLYL-N)-PROPIONIC ACID IN *CITRULLUS VULGARIS*

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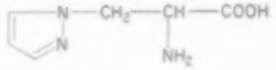
Abstract—The structure of the amino acid, L-α-amino-β-(pyrazolyl-N)-propionic acid, isolated from the semen of the water melon, *Citrullus vulgaris*, has been confirmed by synthesis.

α-AMINO-β-(PYRAZOLYL-N)-PROPIONIC acid, isolated from the semen of *Citrullus vulgaris*, is so far the only naturally occurring amino acid with a pyrazole structure and with the alanine group directly attached to the N of the heterocyclic ring.

Shinano *et al.*[1] isolated the amino acid (I) from the juice of *Citrullus vulgaris* and assumed the structure to be either α-amino-α-(imidazolyl-N)-propionic acid or α-amino-β-(imidazolyl-N)-propionic acid. Later, Fowden *et al.*[2] proposed the correct structure for I on partially convincing evidence and this hypothesis has now been confirmed by synthesis.

Pyrazole is readily synthesized in good yield by the reaction of tetramethoxypropane with hydrazine sulphate. The sodium salt of pyrazole was condensed with bromethylacetal in xylene yielding α-(pyrazolyl-N)-acetaldehyde. Addition of ammonium cyanide and subsequent hydrolysis according to the Strecker synthesis gave DL-α-amino-β-(pyrazolyl-N)-propionic acid. The latter was resolved after acetylation by addition of acylase from *Aspergillus oryzae* according to Chibata *et al.*[3] As only the L-acid is deacetylated, the L-amino acid may be separated from the mixture. This synthetic L-α-amino-β-(pyrazolyl-N)-propionic acid is identical in every respect with the naturally occurring compound isolated from the semen of *Citrullus vulgaris*.



I

EXPERIMENTAL

Pyrazole. A mixture of tetramethoxypropane (297 g) and hydrazine sulphate (214 g) was heated with stirring for 3 hr. The reaction mixture was concentrated to ½ volume under reduced press, neutralized with sodium carbonate, ether extracted, dried and evaporated. The residual oil was purified by vacuum distillation giving pyrazole (68 g; 62%) b.p. 108–110°/45 mm and crystallized from benzene in needles m.p. 70°.

Diethyl-α-(pyrazolyl-N)-ethylacetal. To sodium amide solution, prepared from sodium (23 g) in ammonium hydroxide (200 cc) and ferrous nitrate (0·02 g), pyrazole (70 g) was added and stirring continued for 30 min. Xylene (200 cc) was added and the solution warmed until the ammonia had

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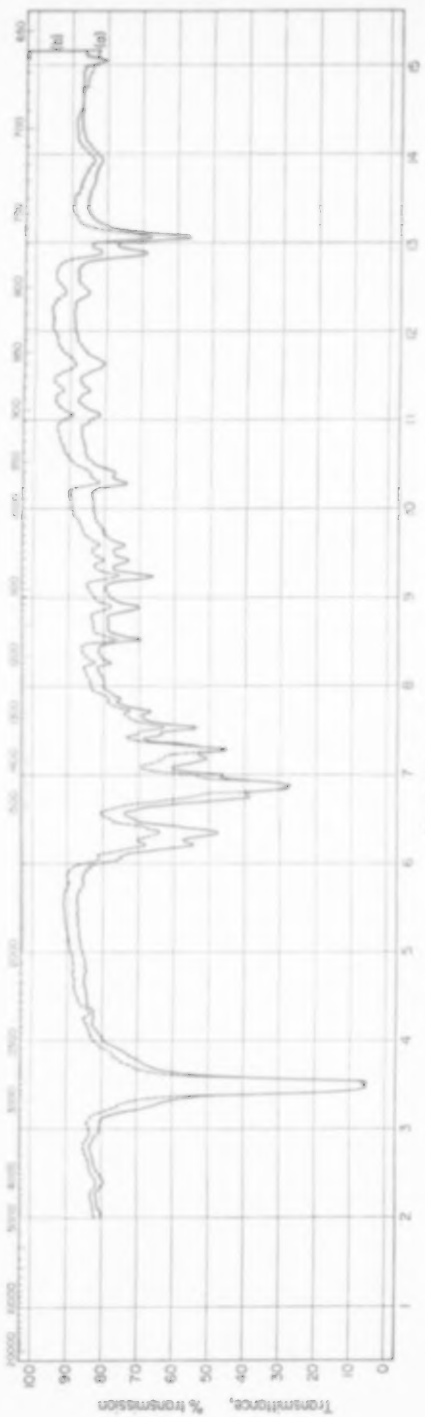

FIG. 1. I. R. spectra of synthesized and natural amino acids.
(a) Synthesized.
(b) Natural

been completely eliminated. The sodium pyrazole in xylene was refluxed for 10 hr with diethyl-α-bromethylacetal (220 g) and after cooling the xylene layer washed with water, dried and evaporated under reduced press. The yield of diethyl-α-(pyrazolyl-N)-ethylacetal, b.p. 112–119°/23 mm was 56·3 g (32·4%) and bromacetal (43 g) was recovered. (Found: C, 58·27; H, 8·58; N, 13·94. $C_9H_{16}N_2O_2$ requires: C, 58·67; H, 8·75; N, 14·21%).

α-(*Pyrazolyl*-N)-*acetaldehyde*. Diethyl-α-(pyrazolyl-N)-ethylacetal (20 g) was added to 5% HCl (100 cc) at 90–95° and the temp maintained for 5 min. The solution was cooled rapidly with ice water, the pH adjusted to 7·0 with sodium bicarbonate, extracted with chloroform, dried, evaporated

R_f VALUES OF SYNTHESIZED AND NATURAL AMINO ACIDS

Solvent used	R_f Values	
	Synthesized	Natural
BuOH : AcOH : H_2O (4:2:1)	0·42	0·41
BuOH : AcOH : H_2O (2:2:1)	0·45	0·45
PhOH : 0·1% NH_3 aq. sol. (4:1)	0·74	0·73

and distilled under reduced press in an atmosphere of nitrogen, yielding α-(pyrazolyl-N)-acetaldehyde 7·4 g (59%) b.p. 66–70°/0·7 mm. The 2,4-dinitrophenylhydrazone crystallized from ethanol in yellow needles m.p. 173–173·5°. (Found: C, 45·56; H, 3·85; N, 28·97. $C_{11}H_{10}O_4N_6$ requires: C, 45·52; H, 3·47; N, 28·96%).

DL-α-*Amino*-β-(*pyrazolyl*-N)-*propionic acid*. α-(Pyrazolyl-N)-acetaldehyde (22·8 g) in ether (100 cc) was saturated with dry ammonia at 0° and the resulting solution allowed to stand overnight. The residue, after evaporation of the ether, was dissolved in a small portion of water, 12% HCN solution (48·3 cc) added and stirring continued at room temp for 10 hr. The aminonitrile was hydrolysed by refluxing with 25% HCl (210 cc) for 2 hr, the solution was evaporated to dryness under reduced press, the residue dissolved in water and decolourized with animal charcoal. Ammonium hydroxide was added to the filtrate till pH 7·0 and an equal volume of ethanol added. The product, (2·1 g; 9·5%) crystallized from water in colourless plates m.p. 243–244°. (Found: C, 46·58; H, 6·01; N, 26·87. $CH_9O_2N_3$ requires: C, 46·44; H, 5·85; N, 27·07%).

DL-α-*Acetamino*-β-(*pyrazolyl*-N)-*propionic acid*. The DL-amino acid (1·7 g) dissolved in 10% NaOH (4·4 cc) was acetylated with acetic anhydride (1·34 g) and 10% NaOH (5·2 cc) in the usual manner yielding the acetyl derivative as colourless needles (1·4 g) from water m.p. 153–153·5°. (Found C, 48·76; H, 5·54; N, 20·94. $C_5H_{11}O_3N_3$ requires: C, 48·72; H, 5·62; N, 21·31%).

L-α-*Amino*-β-(*pyrazolyl*-N)-*propionic acid*. The DL-acetamino acid (1·2 g) was dissolved in water (6 cc) and the pH adjusted to 7·2 with 2N NaOH. To this solution, 5×10^{-4} mole cobaltous chloride (0·6 cc), crude acylase (32 mg; extracted from *Aspergillus oryzae* with water and precipitated by addition of an equal volume of acetone) and a drop of toluene was added. After incubation at 37° for 50 hr, the pH was adjusted to 5 with dil HCl and the mixture boiled for 5 min to coagulate the protein, filtered and concentrated to 1/3 volume under reduced press. Ethanol (10 cc) was added and the solution allowed to stand overnight, yielding L-α-amino-β-(pyrazolyl-N)-propionic acid (200 mg) which crystallized from water in colourless plates m.p. 243–244° (decomp). (Found: C, 45·86; H, 5·52; N, 26·78. $C_6H_9O_2N_3$ requires: C, 46·44; H, 5·85; N, 27·07%). The synthetic L-α-amino-β-(pyrazolyl-N)-propionic acid is identical in all respects with the natural product.

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SYNTHESIS OF 1,3-DIMETHYL-1,3-DICARBOXYCYCLOHEXANE-2-ACETIC ACID

AN ISOMER OF THE DEGRADATION PRODUCT OF ABIETIC ACID[1]

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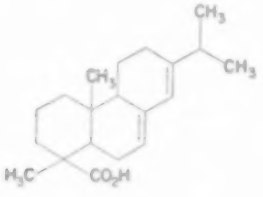
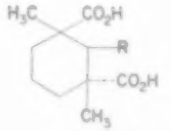
Abstract—A synthesis of 1,3-dimethyl-1,3-dicarboxycyclohexane-2-acetic acid has been described, and proved to be an isomer of the C_{12}-acid—an oxidative degradation product of abietic acid.

ABIETIC acid (I) yields two optically inactive homologous tricarboxylic acids,[2-5] $C_{11}H_{16}O_6$ (II) and $C_{12}H_{18}O_6$ (III), on energetic oxidation with potassium permanganate or vigorous ozonolysis[6,7] and oxidation with nitric acid.[8] The stereochemistry of the



I



II, R = CO_2H
III, R = CH_2CO_2H

C_{11}- and C_{12}-acids has played a very important part in determining the configuration of ring A and B of abietic acid (I) and related resin acids. Barton and Schmeidler[5] assigned the *trans–meso* configuration to these acids (II and III) on the basis of the thermodynamic dissociation constant and optical inactivity.[9]

Although various attempts to synthesize the C_{12}-acid have been recorded,[10,11] final confirmation of its structure by synthesis still remains to be achieved. The

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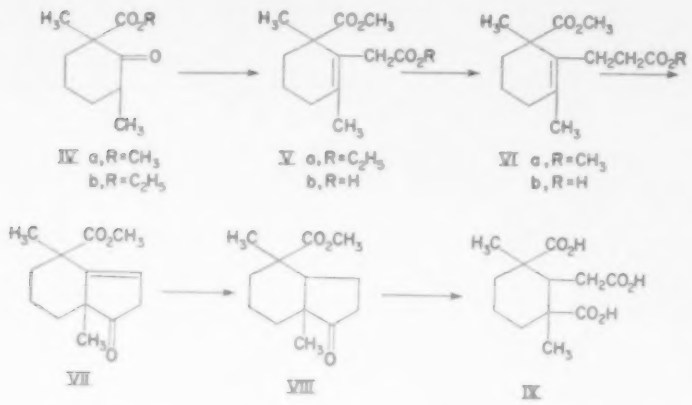
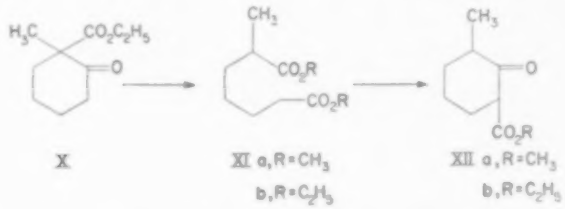


present paper deals with an investigation on the synthesis of the C_{12}-acid by the method outlined below.

Methyl 2,6-dimethylcyclohexanone-2-carboxylate (IVa) was employed as the starting material. The corresponding ethyl ester (IVb) was first prepared by Ruzicka *et al.*[12] and later by Haworth and Barker[13] by methylation of ethyl 6-methylcyclo-



hexanone-2-carboxylate (XIIb), the latter being prepared by the method of Kotz *et al.*[14] In the present investigation a different procedure, as outlined below, was adopted for the preparation of XIIa. Ethyl 2-methylcyclohexanone-2-carboxylate[15] (X) on treatment with sodium ethoxide yielded diethyl α-methylpimelate[16] (XIb), contaminated with presumably the β-keto ester (XIIb) giving colour with alcoholic ferric chloride. As it was not possible to separate the two by fractional distillation, the crude product was treated with 10 per cent aqueous methanolic potassium hydroxide with the expectation that, besides saponification, the contaminating β-keto ester would undergo ketonic fission by this treatment. The resulting acidic material was esterified to yield the pure dimethyl α-methylpimelate (XIa) in 60 per cent overall yield. Dieckmann cyclization of XIa, using sodium dust, furnished methyl 6-methylcyclohexanon-2-carboxylate (XIIa) in 45 per cent yield; the use of sodium hydride increased the yield to 90 per cent. The β-keto ester (XIIa) was methylated with sodium dust and methyl iodide in benzene to give methyl 2,6-dimethylcyclohexanone-2-carboxylate (IVa) in 95 per cent yield.

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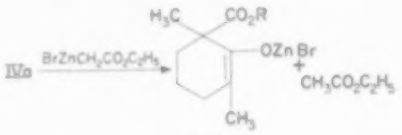
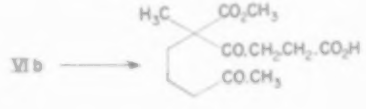
The keto ester (IVa) was subjected to Reformatsky reaction using equivalent quantities of ethyl bromoacetate and zinc wool in presence of a crystal of iodine. After decomposition of the resulting complex the crude condensation product was obtained in 30 per cent yield, and 60 per cent of the keto ester (IVa) was recovered. Use of larger quantities[17] of ethyl bromoacetate and zinc did not have any appreciable effect on the yield. This was probably due to the simultaneous formation of an enolate complex (XIII), analogous to the observation of Newman[18]. Hence, it was found



XIII

expedient to use equimolecular proportions of the reactants and repeat the experiment several times with the recovered keto ester. The crude condensation product was dehydrated using thionyl chloride and pyridine to yield ethyl 2,6-dimethyl-6-carbomethoxycyclohexene-1-acetate (Va) in 68 per cent yield. The dehydrated product consisted mainly of the β,γ-isomer (Va), indicated by the absence of the characteristic ultra-violet absorption maximum of the acrylic ester system.[19] The unsaturated diester (Va) was partially saponified by treatment with one equivalent of 10 per cent aqueous methanolic potassium hydroxide to yield 2,6-dimethyl-6-carbomethoxycyclohexene-1-acetic acid (Vb). The acid chloride, obtained from Vb by treatment with oxalyl chloride,[20] was converted into methyl 2,6-dimethyl-6-carbomethoxycyclohexene-1-β-propionate (VIa) in 50 per cent yield by treatment with diazomethane[21] followed by Wolff rearrangement[22] of the crude diazoketone. The diester (VIa), thus obtained, was partially saponified to give 2,6-dimethyl-6-carbomethoxycyclohexene-1-β-propionic acid (VIb). Evidence for the γ,δ-ethylenic linkage in 2,6-dimethyl-6-carbomethoxycyclohexane-1-β-propionic acid (VIb) was provided by ozonolysis[23] of VIb-which yielded a diketo acid (XIV) identified through its bis-2,4-dinitrophenylhydrazone. In this reaction no neutral aldehydic or ketoester could be detected indicating



XIV

the absence of β,γ- or α,β-ethylenic linkage. Cyclization of the homologous ester acid (VIb) was carried out with phosphorus pentoxide[24] in refluxing benzene to yield 4,8-dimethyl-4-carbomethoxy-Δ^3-hydrindene-1-one (VII) in 40 per cent yield. The unsaturated keto ester (VII) did not show any ultra-violet absorption maximum

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characteristic of Δ^2-cyclopentenone derivative[25] and hence was assigned the structure VII. Catalytic reduction of VII yielded 4,8-dimethyl-4-carbomethoxy-hydrindane-1-one (VIII) as a colourless mobile oil. Barton[26] had shown that among 1,2,2,6,6-pentasubstituted derivatives of cyclohexanes the axial substituent at C_1 is less hindered than the equatorial substituent, and assuming that the heavier carbomethoxyl group was equatorial and the methyl group axial we considered that the hydrogen might approach from the less hindered[27] axial side giving a *trans*-hydrindanone derivative. On the other hand, on account of hindrance due to the axial methyl groups,[28] the hydrogen might approach from the equatorial side leading to a *cis*-hydrindanone ring system. Consequently, the triacid (IX), obtainable by oxidation of the reduced keto ester (VIII), could be either *trans–meso* or *cis–meso* or a mixture of the two depending on the mode of hydrogenation of the unsaturated keto ester (VII). The saturated keto ester (VIII) was condensed with ethyl formate to yield the corresponding hydroxymethylene derivative which was oxidized[29] in the crude state with hydrogen peroxide to yield 1,3-dimethyl-1-carbomethoxy-3-carboxycyclohexane-2-acetic acid, and this was directly saponified[30] with 25 per cent aqueous methanolic potassium hydroxide to give 1,3-dimethyl-1,3-dicarboxycyclohexane-2-acetic acid (IX) as a solid. It was crystallized from acetone to give clusters of very fine needles, m.p. 212–213°(d). The mixed melting point, however, was depressed by 8° on admixture with the C_{12}-acid, m.p. 212–213°, obtained by the degradation of abietic acid,[5,8] thus indicating the synthetic acid to be a stereoisomer having, presumably, a *cis–meso* configuration. Rao and Bagchi[11] also obtained an isomer melting at the same temperature, which is in all probability identical with our product.

EXPERIMENTAL*

Dimethyl α-methylpimelate (XIa). Ethyl 2-methylcyclohexanone-2-carboxylate[15] (X, 184 g) and a solution of sodium ethoxide, prepared from sodium (4·6 g) and ethanol (58 ml), were heated for 4 hr on a steam bath. To the reaction mixture, which gave ferric chloride colouration, was added 10% aqueous methanolic KOH (2 l.) and the mixture was refluxed for 5 hr. The methanol was removed under reduced press and the aqueous solution of the residue, after one extraction with ether, was acidified with cold dil HCl. The oily product was extracted with ether, and the ether extract was washed with water and dried (Na_2SO_4). After removal of the solvent, the crude acidic product was esterified by refluxing for 72 hr with methanol (900 ml) containing conc H_2SO_4 (90 ml). The cooled reaction mixture was poured into ice cold brine and worked up by extraction with ether in the usual way. Removal of the solvent and distillation of the residue *in vacuo* furnished XIa (120 g, 60%), b.p. 98–100° (1 mm), n_D^{27} 1·4320. (Found: C, 59·30; H, 8·83. $C_{10}H_{18}O_4$ requires: C, 59·40; H 8·91%).

Methyl 6-methylcyclohexanone-2-carboxylate (XIIa). A small portion (ca. 10 g) of dimethyl α-methylpimelate (XIa, 107 g) was added to refluxing benzene (500 ml) suspension of sodium hydride (23 g) in an atmosphere of nitrogen. After the reaction started (ca. 30 min), the rest of the diester was slowly added and the refluxing continued for 4 hr. The cooled reaction mixture was decomposed with an excess of cold dil HCl under nitrogen. The organic layer was separated and washed

* All m.ps and b.ps are uncorrected, and all ultra-violet measurements were taken in 95% ethanol with a Beckmann Quartz Ultra-violet Spectrophotometer, Model DU.

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successively with water, ice cold aqueous $NaHCO_3$, and water. The solvent was removed and the residue distilled to give XIIa (82 g, 90%), b.p. 65–68° (1 mm), n_D^{25} 1·4768. (Found: C, 63·51; H, 8·35. $C_9H_{14}O_3$ requires: C, 63·53; H, 8·23%).

When the aforementioned reaction was carried out using sodium dust the β-keto ester (XIIa) was obtained in 45% yield.

Methyl 2,6-*dimethylcyclohexanone*-2-*carboxylate* (IVa). Methyl 6-methylcyclohexanone-2-carboxylate (XIIa, 162 g) was slowly added to an ice cold suspension of sodium dust (23·06 g) in dry benzene (1 l.) and allowed to stand overnight. To the sodio derivative thus formed was added methyl iodide (150 ml), and the mixture was refluxed till it did not give any colour with alcoholic ferric chloride (ca. 6 hr). It was poured into water and the benzene layer was separated. The aqueous layer was extracted with ether and the combined ether–benzene mixture was washed with water and dried (Na_2SO_4). The solvent was removed and the residue distilled to yield IVa (165 g, 95%), b.p. 81–82° (1 mm), n_D^{24} 1·4571. (Found: C, 65·25; H, 8·59. $C_{10}H_{16}O_3$ requires: C, 65·22; H, 8·69%).

Ethyl 2,6-*dimethyl*-6-*carbomethoxycyclohexene*-1-*acetate* (Va). A solution of methyl 2,6-dimethylcyclohexanone-2-carboxylate (IVa, 60 g) and ethyl bromoacetate (56 g) in thiophene-free dry benzene (200 ml) was slowly distilled until about 30 ml of benzene was collected to remove the last traces of moisture. This was cooled to the room temp with protection from moisture and zinc wool[31] (22 g) and a crystal of iodine were added. On heating the mixture on a steam bath an exothermic reaction ensued, and the vigour of the reaction was maintained as far as practicable by continuing the heating. Subsequently the reflux was continued for 4 hr. The cooled reaction mixture was decomposed with ice-cold dil H_2SO_4. The benzene solution was separated and the aqueous layer was extracted with ether–benzene mixture. The combined ether–benzene extract was washed successively with water, ice-cold dil NH_4OH and finally with water. After drying (Na_2SO_4) the solvent was removed. The residue was distilled to recover the starting keto ester (IVa, 43 g), and the crude condensation product weighed 20 g. The aforementioned Reformatsky reaction was repeated 3 times using the recovered keto ester from each experiment, thus yielding a total quantity of 36 g of the crude condensation product. To a vigorously stirred, cooled (0°) solution of the aforementioned condensation product and pyridine (21 g) in dry ether (100 ml) was added thionyl chloride (10 ml) over a period of 1 hr, the temp being kept below 5°. The reaction mixture was left overnight at room temp. The ethereal layer was decanted off and the dark residue after repeated washing with dry ether was diluted with a large volume of water, filtered from the slimy residue, and worked up by extraction with ether in the usual manner. The solvent was removed on a steam bath and finally under reduced press. The residue was taken up in dry benzene (100 ml) and refluxed for 5 hr with freshly precipitated copper to remove the contaminating sulphur. After removal of the benzene from the filtered solution, the residue was distilled to yield Va (23 g, 68%), b.p. 115–118° (1 mm), n_D^{25} 1·4753. (Found: C, 66·08; H, 8·63. $C_{14}H_{22}O_4$ requires: C, 66·15; H, 8·68%).

2,6-*Dimethyl*-6-*carbomethoxycyclohexene*-1-*acetic acid* (Vb). Ethyl 2,6-dimethyl-6-carbomethoxycyclohexene-1-acetate (Va, 13 g) was refluxed for 4 hr with aqueous methanolic KOH (31 ml, 1·624 N). The methanol was removed under reduced press and the residue was dissolved in water. The aqueous solution, after one extraction with ether, was acidified with cold dil HCl. The oily product was extracted with ether and the extract washed with water and dried (Na_2SO_4). After removal of the solvent, the product was distilled, b.p. 155–160° (0·5 mm), to yield an oil which subsequently solidified. It was crystallized from acetone to furnish Vb (8 g, 69%), m.p. 123–124·5° (Found: C, 63·66; H, 7·95. $C_{12}H_{18}O_4$ requires: C, 63·72; H, 7·96%).

The S-*benzylthiuronium salt* of Vb crystallized from dil ethanol, m.p. 129–130° (Found: N, 7·20. $C_{20}H_{28}N_2O_4S$ requires: N, 7·14%).

Methyl 2,6-*dimethyl*-6-*carbomethoxycyclohexene*-1-β-*propionate* (VIa). To an ice-cold solution of 2,6-dimethyl-6-carbomethoxycyclohexene-1-acetic acid (Vb, 10 g) in dry benzene was added oxalyl chloride[32] (9 ml). After keeping at room temp for 4 hr, the mixture was warmed for 10 min at 45°. The benzene along with excess of oxalyl chloride were removed under reduced press. Fresh dry benzene (10 ml) was added and distilled off under *vacuo* to remove the last traces of oxalyl chloride. A solution of the crude acid chloride (10 g) in dry ether (50 ml) was added to a cold (0°) anhydrous ethereal solution of CH_2N_2, prepared from nitrosomethyl urea[33] (23 g), with stirring over a period of

[31] R. L. Shriner, *Org. Reactions* **1**, 1 (1942).
[32] H. Staudinger, *Ber. Dtsch. Chem. Ges.* **41**, 3558 (1908).
[33] F. Arndt, *Org. Syntheses* Vol. II, p. 165 (1950).

1 hr, when the evolution of nitrogen stopped. The solvent and excess of CH_2N_2 were removed under reduced press at room temp to yield the oily diazo ketone (12 g).

To a warm (50°), stirred solution of the crude diazo ketone (12 g) in absolute methanol (300 ml) was added in 3 lots a slurry of silver oxide in methanol, obtained from 10% aqueous $AgNO_3$ (50 ml). The mixture was refluxed for 2 hr, and after boiling with norite was filtered. The alcohol was removed under reduced press and the residue was distilled to yield VIa (5 g, 50%), b.p. 125–130° (1 mm), n_D^{25} 1·4820. (Found: C, 66·36; H, 8·66. $C_{14}H_{22}O_4$ requires: C, 66·15; H, 8·68%).

2,6-Dimethyl-6-carbomethoxycyclohexene-1-β-propionic acid (VIb). Methyl 2,6-dimethyl-6-carbomethoxycyclohexene-1-β-propionate (VIa, 8 g) was partially saponified as before by refluxing with 10% aqueous methanolic KOH (18 ml, 1·624 N) for 4 hr and worked up as usual to yield VIb (5 g, 76%). It was crystallized from acetone, m.p. 143–144·5°. (Found: C, 64·98; H, 8·23. $C_{13}H_{20}O_4$ requires: 65·00; H, 8·33%).

The *S-benzylthiuronium salt* of VIb crystallized from dil ethanol, m.p. 141–142°. (Found: N, 7·03. $C_{21}H_{30}N_2O_4S$ requires: N, 6·89%).

Ozonolysis of 2,6-dimethyl-6-carbomethoxycyclohexene-1-β-propionic acid (VIb). To a cooled (0°) solution of the unsaturated ester acid (VIb, 0·2 g) in carbon tetrachloride (50 ml) was passed a current of ozonized oxygen for 30 min. The solvent was removed and the residue was heated for 15 min on a steam bath with a mixture of zinc dust (0·4 g), water (15 ml), and acetic acid (0·7 ml). The reaction mixture was extracted with ether and the ethereal solution was extracted thoroughly with 5% ice-cold NaOH. The acidic material was isolated as an oil by acidification of the alkaline extract followed by extraction with ether and was converted to the *bis-2,4-dinitrophenylhydrazone* of 5-carbomethoxy-4,9-dioxo-5-methyldecanoic acid (XIV) by the usual method. It was crystallized from alcohol, m.p. 185–186°. (Found: N, 17·70. $C_{25}H_{28}N_8O_{12}$ requires: N, 17·72%).

On removal of the ether from the neutral fraction no product could be isolated.

4,8-Dimethyl-4-carbomethoxy-Δ³-hydrindene-1-one (VII). To a vigorously stirred, refluxing solution of P_2O_5 (20 g) in benzene (100 ml) was added a solution of 2,6-dimethyl-6-carbomethoxycyclohexene-1-β-propionic acid (VIb, 3 g) in dry benzene (80 ml) over a period of 30 min, and the refluxing was continued for 3 hr. The reaction mixture was cooled and the benzene was decanted off. The dark residue after repeated washing with benzene, was decomposed with powdered ice, diluted with a large volume of water, filtered from the slimy residue, and extracted with ether. The combined ether–benzene extract was washed successively with water, 10% aqueous NaOH, water, and dried (Na_2SO_4). The solvent was removed and the residue distilled to furnish VII (1·2 g, 43%), b.p. 100–105° (0·6 mm), n_D^{25} 1·4830. (Found: C, 70·70; H, 8·40. $C_{13}H_{16}O_3$ requires: C, 70·26; H, 8·10%).

4,8-Dimethyl-4-carbomethoxyhydrindane-1-one (VIII). A solution of the aforementioned unsaturated keto ester (VII, 1·2 g) in ethanol (15 ml) was hydrogenated with prereduced platinum oxide catalyst (0·1 g). After absorption of the calculated quantity of hydrogen (ca. 24 hr) the catalyst was removed by filtration followed by the removal of the solvent. The residue was purified by shortpath distillation to yield VIII (1 g, 83%), 110–115° (bath temp) (1 mm), n_D^{25} 1·4685. (Found: C, 69·60; H, 8·99. $C_{13}H_{20}O_3$ requires: C, 69·65; H, 8·93%).

1,3-Dimethyl-1,3-dicarboxycyclohexane-2-acetic acid (IX). To a vigorously stirred ice-cold suspension of sodium ethoxide in dry benzene, prepared from sodium (0·2 g) and absolute ethanol (0·4 g), was added ethyl formate (1 g) under nitrogen. After 30 min a solution of the saturated ketone (VIII, 1 g) in dry benzene (10 ml) was added, and the mixture was left overnight at room temp. After adding ice-cold water to the cooled reaction mixture, the aqueous layer was separated and the benzene layer was thoroughly extracted with 2% ice-cold aqueous NaOH. The combined aqueous solution, after one extraction with ether, was acidified with ice-cold dil HCl. The resulting oily suspension was extracted with ether and the crude hydroxymethylene ketone (0·8 g), obtained after removal of the solvent, gave violet colour with alcoholic ferric chloride.

To a solution of the aforementioned crude hydroxymethylene ketone (0·8 g) in ethanol (2 ml) and 2 N NaOH (30 ml) was added 30% hydrogen peroxide (9 ml), and the mixture was allowed to stand at the room temp for 1 hr. It was next heated under reflux for 2 hr followed by two more similar treatments with hydrogen peroxide. The solvent was removed under reduced press, and the aqueous solution of the residue, after one extraction with ether, was acidified with cold dil HCl. The oily product was worked up by extraction with ether. After removal of the solvent, the crude ester diacid (0·4 g) was saponified by refluxing for 5 hr at 150° with 25% aqueous methanolic KOH (8 ml). The methanol was removed under reduced press and the aqueous solution of the residue, after one

extraction with ether, was acidified with cold dil HCl. The resulting oily suspension was worked up by extraction with ether. While removing the solvent, the triacid crystallized out as a white solid IX (0·1 g, 10%). It was crystallized from acetone, m.p. 212–213° (d). (Found: C, 56·01; H, 7·07. $C_{12}H_{14}O_6$ requires: C, 55·82; H, 7·09%).

Acknowledgements—We wish to record our thanks to Messrs. B. R. Seetharamia and D. P. Bose for the microanalyses and to the Government of Orissa and the Government of India for the award of a scholarship to one of us (S. N. M.).

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ZUR ACYLIERUNG VON 5-ARYL-TETRAZOLEN; EIN DUPLIKATIONSVERFAHREN ZUR DARSTELLUNG VON POLYARYLEN*

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Zusammenfassung—5-Substituierte 2-Acyl-tetrazole erleiden bei 60–110° eine Thermolyse unter Stickstoffaustritt. Die N-Acyl-nitrilimine als hypothetische Zwischenstufen schliessen den 1,3,4-Oxdiazolring mit sehr guter Ausbeute. Die abwechselnde Behandlung des 5-Phenyl-tetrazols mit *p*-Cyan-benzoylchlorid und mit Lithiumazid bietet ein elegantes Duplikationsverfahren zum Aufbau von Polyarylen mit alternierenden Benzol- und 1,3,4-Oxdiazolkernen. Vom Terephthalsäure-dinitril aus werden in 4 Reaktionsstufen neunkernige Polyaryle erreicht. In der Lichtabsorption entspricht das 2,5-disubstituierte 1,3,4-Oxdiazol einer *p*-Phenylen-Einheit.

Abstract—We have found that the thermolysis of 5-substituted 2-acyl-tetrazoles (I) at 60–110° leads to quantitative loss of nitrogen and formation of an N-acyl-nitrilimine (III) as a hypothetical intermediate. This immediately reacts via ring closure to form 1,3,4-oxadiazoles (IV) in excellent yields. By an elegant reaction series it is possible to form polyaryles with alternating phenyl and 1,3,4-oxadiazole rings by repeated reaction of 5-phenyltetrazole with *p*-cyano-benzoylchloride followed by treatment with lithium azide. Starting with terephthalonitrile polyaryles possessing 9 rings were synthesized in 4 steps. The ultra-violet absorption of the 2,5-disubstituted 1,3,4-oxadiazole systems resembles very closely the absorption curve of a *p*-disubstituted phenyl-group.

(A) *Ringöffnungen in der Azol-Reihe*

KONDENSIERTE aromatische Kohlenwasserstoffe gehören zu den temperaturbeständigsten organischen Verbindungen. Allerdings kann von einem allgemeinen Zusammenhang zwischen thermischer Beständigkeit und aromatischem Bindungssystem keine Rede sein. Die aufgrund thermochemischer Daten zweifellos aromatischen Aryl-*pentazole* bieten das andere Extrem; nach Huisgen und Ugi[1] beträgt die Halblebenszeit des Phenyl-pentazols in Methanol bei 0° nur 13 Min.

Tetrazol und seine Derivate sind dem Pentazol in der Temperaturbeständigkeit überlegen, erreichen aber bei weitem nicht die der Benzol-Abkömmlinge. Während

* Ringöffnungen der Azole, III; Mitt. II, R. Huisgen, J. Sauer, H. J. Sturm und J. H. Markgraf, *Chem. Ber.* **93**, 2106 (1960).

† Diplomarbeit H. J. Sturm, Universität München 1958; Dissertation, ebenda 1960.

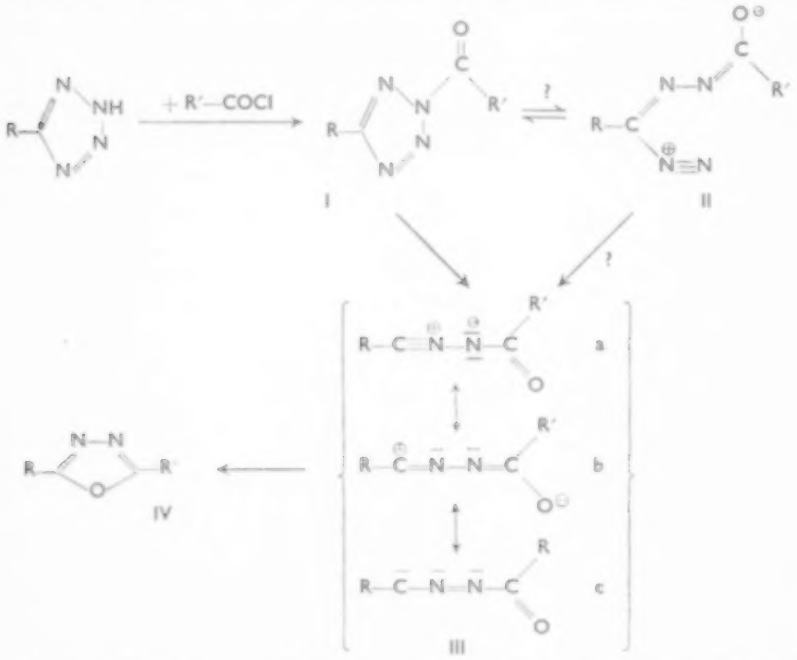
[1] R. Huisgen und I. Ugi, *Angew. Chem.* **68**, 705 (1956); *Chem. Ber.* **90**, 2915 (1957). Vgl. ferner I. Ugi und R. Huisgen, *Ibid.* **91**, 531 (1958); I. Ugi, H. Perlinger und L. Behringer, *Ibid.* **91**, 2324 (1958); *Ibid.* **92**, 1864 (1959).

das 5-Phenyl-tetrazol am Schmelzpunkt (215°) Stickstoff freisetzt,[2] sind die Alkalisalze der Tetrazole viel stabiler. Immerhin konnte man aus Isomerisierungen in der Reihe des 5-Amino-tetrazols schliessen, dass schon bei 140° eine kleine Gleichgewichtskonzentration an offenkettigen Guanylaziden vorliegt.[3]

Man darf erwarten, dass die Öffnung aromatischer Ringe umso leichter erfolgt, je besser der Verlust an Bindungsenergie—dieser ist auch die aromatische Resonanzenergie zuzurechnen—schon im Übergangszustand kompensiert wird. Die Verfolgung dieses Gedankenganges führte zur Aufdeckung *neuer Ringöffnungen in der Azol-Reihe*, die zum Teil bereits bei recht niedriger Temperatur ablaufen.[4] Wir fanden, dass sich an die Acylierung 5-substituierter Tetrazole mit Carbonsäure-chloriden oder-anhydriden schon bei 60–120°, je nach Substitution, eine Stickstoffentwicklung anschliesst; in sehr guten Ausbeuten wurden 2,5-disubstituierte 1,3,4-Oxdiazole isoliert.[5]

Kinetische Versuche kennzeichneten dabei die Acylierung der Tetrazol-Derivate in der Stellung 2 als rasche, vorgelagerte Reaktion; in günstigen Fällen liessen sich die Acyl-tetrazole (I) quantitativ isolieren.

Die aromatische Tetrazol-Mesomerie beansprucht das Elektronenpaar am N-2 in



I so stark, dass die Carbonamid-Mesomerie geschwächt erscheint. Eine hohe Aktivität der Acyl-tetrazole als Acylierungsmittel[6] sowie sehr kurzwellige infrarote Carbonylschwingungen in I (1780–1800/cm)[5] sind die Folge. Die Ringöffnung erfährt eine

[2] W. Lossen und F. Statius, *Liebigs Ann.* **298**, 91 (1897).
[3] W. G. Finnegan, R. A. Henry und E. Lieber, *J. Org. Chem.* **18**, 779 (1953); W. L. Garbrecht und R. M. Herbst, *Ibid.* **18**, 1269 (1953); R. A. Henry, W. G. Finnegan und E. Lieber, *J. Amer. Chem. Soc.* **76**, 88 (1954); *Ibid.* **77**, 2264 (1955).
[4] Übersicht: R. Huisgen, *Angew. Chem.* **72**, 359 (1960).
[5] R. Huisgen, J. Sauer und H. J. Sturm, *Angew. Chem.* **70**, 272 (1958); R. Huisgen, J. Sauer, H. J. Sturm und J. H. Markgraf, *Chem. Ber.* **93**, im Druck (1960).
[6] H. A. Staab, *Chem. Ber.* **89**, 1927 (1956).

mächtige Förderung durch den Gewinn an Carbonamid-Mesomerie. Ob sich die Sprengung des Tetrazolringes über den Diazoalkan-Abkömmling II als Zwischenstufe vollzieht oder ob der molekulare Stickstoff einstufig abgelöst wird, steht noch nicht fest. Aufgrund kinetischer Untersuchungen[4] bevorzugen wir den Mehrzentrenprozess, der unmittelbar von I zu III führt und von der Freigabe der extrem grossen Bindungsenergie des N_2-Moleküls profitiert. Die hypothetische, aber zwangsläufige Zwischenstufe III ist ein N-Acyl-nitrilimin. Die Sextett-Grenzformeln IIIb und c charakterisieren den zentralen Kohlenstoff als elektrophil und legen den Weg der innermolekularen Stabilisierung durch erneuten Ringschluss zu IV nahe.

In über 50 Beispielen bewährte sich die Tetrazol-Acylierung als ebenso ergiebige wie einfache Synthese von 1,3,4-Oxdiazol-Abkömmlingen.[5] Die Alkyl- oder Arylreste im Tetrazol-Derivat und im Acylierungsmittel erwiesen sich in weiten Grenzen variationsfähig.

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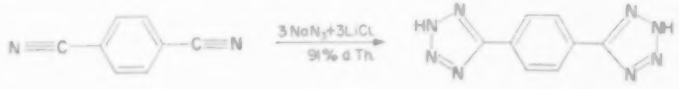
(B) *Darstellung von Polyaromaten mit alternierender Folge von Benzol- und* 1,3,4-*Oxdiazolkernen*

Die hohen Ausbeuten bei der acylierenden Ringöffnung 5-substituierter Tetrazole machten ein Duplikationsverfahren zur Synthese definierter Polyaryle aussichtsreich.

Die Reihen der p- *und* m-*Polyphenyle* finden sich bis zum *p*-Septiphenyl (n = 7) bzw. dem *m*-Sedeciphenyl (n = 16) erschlossen.[7,8] Die meist nicht sonderlich ergiebigen Synthesen sind entweder speziell auf ein Glied der Reihe gerichtet oder sie liefern Gemische von Oligomeren. Zu den letzteren gehört etwa der Zerfall von Benzol-diazoniumsalz in Gegenwart von Ameisensäure und Kupferpulver, der zu Diphenyl bis *p*-Quinquiphenyl führte.[7a] Die Reduktion von *m*-Dibrombenzol mit Palladium und Hydrazinhydrat in methylalkoholischer Kalilauge ergab gar *m*-Polyphenyle mit n = 3–16, die durch mühsame fraktionierte Kristallisation getrennt wurden.[8]

Kern[9] bemühte sich in den letzten Jahren um Synthesen von *p*-Polyphenylen mit Methyl- und Methoxygruppen in definierter Stellung. Die Ullmann-Synthese, der Zerfall bifunktioneller Nitrosoacyl-arylamine und die lithiumorganische Synthese wurden als Reaktionsstufen herangezogen; die Folge von Jodierung und metallorganischer Synthese scheint ein Duplikationsverfahren zu ermöglichen.

Terephthalsäure-dinitril liess sich mit 3 Äquival. Lithiumazid in siedendem Glykol-monomethyläther—wir berichteten jüngst über diese vorteilhafte Tetrazolsynthese[5]—glatt in 1,4-Di-[tetrazolyl-(5)]-benzol (V) überführen.



V

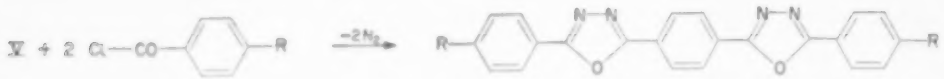
Bei der Einwirkung überschüssigen Benzoylchlorids auf die siedende Suspension von V in wasserfreiem Pyridin wurden glatt 2 Moläquivalente Stickstoff freigesetzt. Die Abscheidung der farblosen Kristalle des fünfkernigen Systems VI setzte schon vor der vollständigen Lösung von V ein. Das 1,4-Di-[2-phenyl-1,3,4-oxdiazolyl-(5)]-

[7] *p*-Polyphenyle: [a] O. Gerngross und M. Dunkel, *Ber. Dtsch. Chem. Ges.* **57**, 739 (1924); [b] R. Pummerer und K. Bittner, *Ibid.* **57**, 84 (1927); R. Pummerer und L. Seligsberger, *Ibid.* **64**, 2477 (1931); [c] M. Busch und W. Weber[8]; [d] E. Müller und T. Töpel, *Ber. Dtsch. Chem. Ges.* **72**, 273 (1939).

[8] *m*-Polyphenyle: M. Busch und W. Weber, *J. Prakt. Chem.* [2] **146**, 1 (1936).

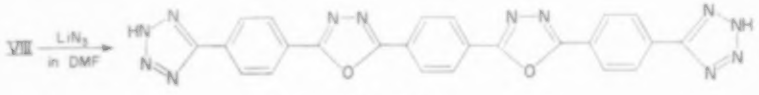
[9] W. Kern, M. Seibel und H. O. Wirth, *Makromol. Chem.* **29**, 164 (1959); W. Kern, H. W. Ebersbach und I. Ziegler, *Ibid.* **31**, 154 (1959); W. Kern, W. Gruber und H. O. Wirth, *Ibid.* **37**, 198 (1960).

benzol (VI) wurde auch durch Cyclisierung des Bis-1,2-diaroyl-hydrazins erhalten.[10] Die aus V mit *p*-Nitrobenzoylchlorid zugängliche Dinitro-Verbindung VII ist noch weniger löslich als VI; aus siedendem Nitrobenzol konnten die gelben Blättchen von VII mit Schmp. 405–406° umgelöst werden.



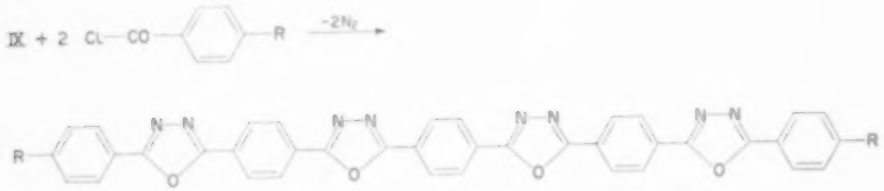
VI R = H 96% d. Th.
VII R = NO_2 98% d. Th.
VIII R = CN 87% d. Th.

Das mit *p*-Cyan-benzoylchlorid aus V analog gewonnene Penta-aryl VIII mit seinen endständigen Nitrilgruppen bietet wieder Gelegenheit zur Angliederung zweier neuer Tetrazolringe. Die Umsetzung mit Lithiumazid gelang in Dimethylformamid in der Siedehitze. Das Auftreten der für Tetrazole charakteristischen assoziierten NH-Valenzschwingung und das Fehlen der Nitrilschwingung sprachen für einen vollständigen Ablauf zum heptacyclischen System IX.



IX 92% d. Th.

Trotz der geringen Löslichkeit setzte sich IX mit überschüssigem Benzoylchlorid bzw. *p*-Cyan-benzoylchlorid in siedendem Pyridin zu den neunkernigen Polyarylen X und XI um. Die Stickstoffentwicklung entsprach nämlich mit 2 Moläquival. der Erwartung. Die Schwerlöslichkeit verhinderte ein Umkristallisieren, jedoch gab das



X R = H 91% d. Th. Schmp. > 465° u. Zers.
XI R = CN 80% d. Th. Schmp. > 480° u. Zers.

mit Lösungsmitteln ausgekochte X richtige Analysenwerte. Das neunkernige Dinitril XI entsprach mit seiner Nitrilbande bei 2230/cm im IR-Spektrum weitgehend dem fünfkernigen Dinitril VIII (Fig. 1). Das Gebiet der aromatischen CH-Waggingschwingungen beansprucht übrigens besondere Aufmerksamkeit. Die Bande des 1,4-d-substituierten Benzolkerns findet sich bei 855 bzw. 856/cm kurzwellig verschoben, wofür wohl die Elektronenanziehung seitens Cyanogruppen und Oxdiazolkernen verantwortlich ist. Die beiden Banden oberhalb 700/cm treten schon bei Diaryloxdiazolen auf; ihre Herkunft ist noch unklar.

[10] F. N. Hayes, B. S. Rogers und D. G. Ott, *J. Amer. Chem. Soc.* **77**, 1850 (1955).

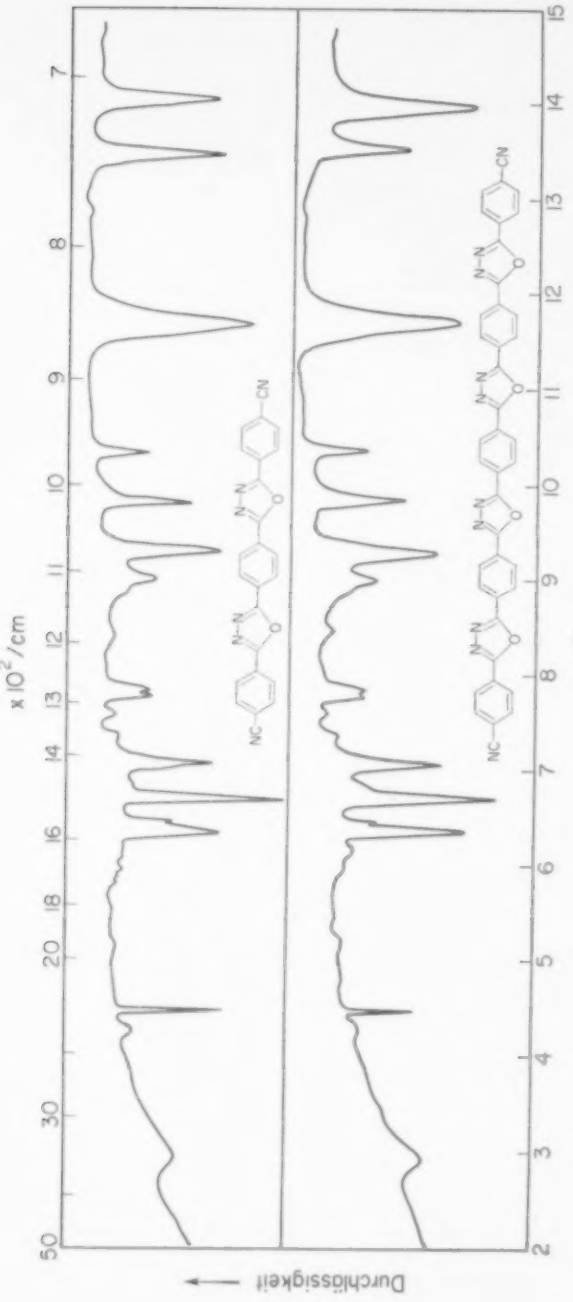


FIG. 1. IR-Spektren der fünf- und neunkernigen Dinitrile VIII und XI (KBr-Presslinge, Leitz-Spektrophotometer).

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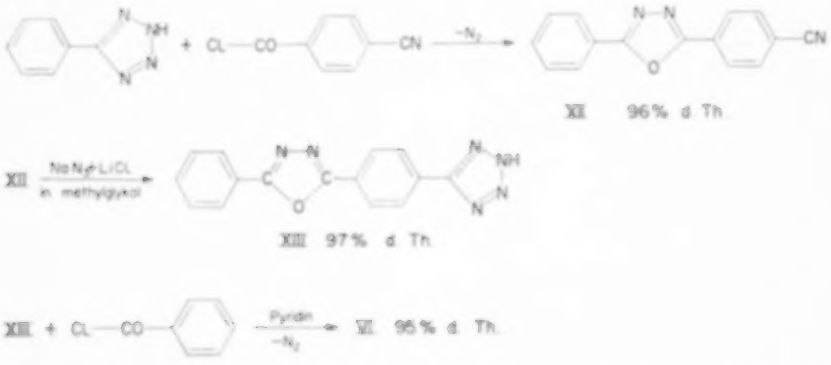
In vier Reaktionsstufen—bei jedem Schritt werden zwei neue aromatische Kerne angegliedert—wurde somit vom Terephthaldinitril aus die nonacyclische Verbindung XI aufgebaut. Ein auch bezüglich der Ausbeuten ähnlich leistungsfähiges Duplikationsprinzip zur Synthese von Polyarylen findet sich nicht beschrieben. Die Gitterenergie, die zu einem Schmelz- bzw. Zersetzungspunkt gegen 480° führt, hat allerdings in XI ein solches Ausmass erreicht, dass kein Lösungsmittel für die erneute Umsetzung der Nitrilgruppen mit Lithiumazid gefunden wurde.

Durch Einbau von Methyl- oder Alkoxygruppen hoffen wir, das Duplikationsverfahren zur Synthese wesentlich höhermolekularer, definierter Polyaryle mit abwechselnden Benzol- und Oxdiazolkernen weiterführen zu können. Kern[9] hat in der Polyphenyl-Reihe die starke Zunahme der Löslichkeit durch Methyl- und Methoxygruppen aufgezeigt. Die höheren Oligomeren von XI sollten gute Modelle zum vergleichenden Studium physikalischer Eigenschaften abgeben.

Auch der einseitige Aufbau von Polyarylen, von 5-Phenyltetrazol und *p*-Cyanbenzoylchlorid ausgehend, liess sich mit sehr guten Ausbeuten verwirklichen. Das folgende Reaktionsschema bedarf keines Kommentars.



Dem Nachteil der Angliederung von nur einem Ring pro Reaktionsschritt steht der Vorteil grösserer struktureller Variation gegenüber. Man gelangt hier auch zu Polyarylen mit gerader Zahl aromatischer Kerne; die Möglichkeit der Bereitung grosser Ringe erscheint prüfenswert.

4-[Tetrazolyl-(5)]-benzoylchlorid (XIV) enthält die beiden zum Oxdiazol-Ringschluss erforderlichen Funktionen in der gleichen Molekel. Die erwartete intermolekulare Wechselwirkung zum Oligo- und Polymeren-Gemisch kam in siedendem Xylol

XIV XV

zustande. Unter Chlorwasserstoff- und Stickstoffabspaltung entstand ein hellbraunes, mikrokristallines Pulver, dessen IR-Spektrum dem der definierten Oligomeren, z.B. X, ähnlich ist. Wir vermuten, dass es sich um ein Gemisch der Polyaryle XV handelt; die nähere Bearbeitung steht noch aus.

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(C) ***Die Lichtabsorption von Polyaromaten mit alternierenden Benzol- und Oxdiazolkernen***

Die Konjugation in *p*-Polyphenylen löst mit steigender Kernzahl (n = 2–6) eine bathochrome Verschiebung der langwelligen Absorptionsbande aus;[11] wie bei Polyenen konvergieren die Bandenmaxima. In der *m*-Polyphenyl-Reihe sollte die Unmöglichkeit chinoider Grenzformeln die Koppelung der π-Systeme drastisch einschränken.

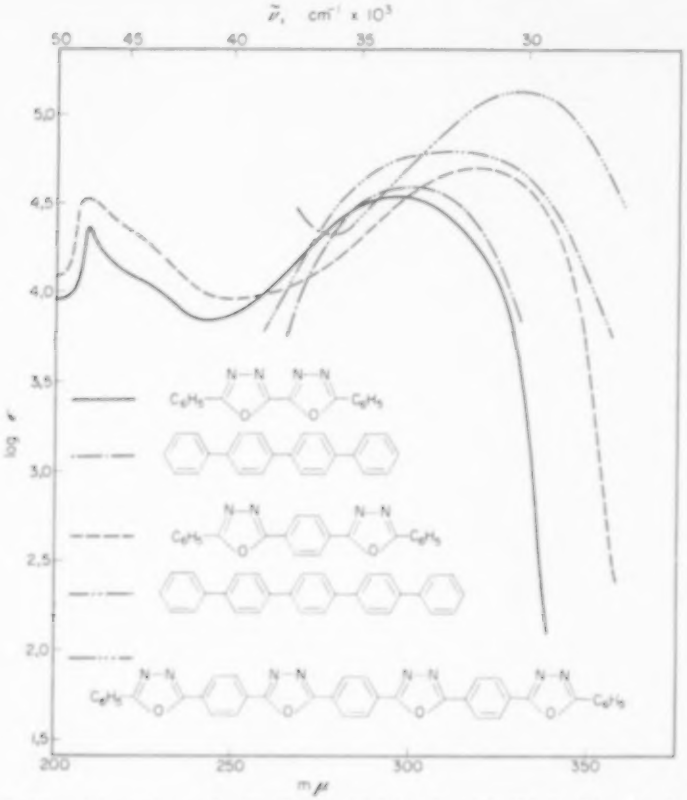


FIG. 2. Ultraviolettspektren des Bis-[2-phenyl-1,3,4-oxdiazolyls-(5)] (in Dioxan), der Polyaryle VI (in Dioxan) und X (in Dimethylformamid) sowie des Quater- und Quinquiphenyls[11] (in Chloroform). Die Extinktion von X wurde willkürlich festgelegt.

Tatsächlich fanden Gillam und Hey[11] das langwellige Absorptionsmaximum lagekonstant von n = 2–16; bei den höheren Gliedern setzt sich die Extinktion additiv aus der der Biphenyl-Bausteine zusammen.

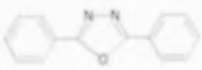
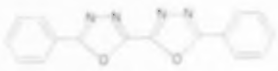
XVI

Über Grenzformeln des Typs XVI sollte der 1,3,4-Oxdiazolkern zur Leitung der

[11] A. E. Gillam und D. H. Hey, *J. Chem. Soc.* 1170 (1939). Zur Theorie vgl. J. N. Murrell und H. C. Longuet-Higgins, *Ibid.* 2552 (1955).

Tabelle 1. Langwellige absorptionsmaxima von *p*-polyphenylen und polyarylen mit alternierenden benzol- und heterocyclischen ringen

Lösungsmittel: a = Äthanol, b = Hexan, c = Dioxan, d = Chloroform, e = Dimethylformamid

	λmax	log ε	Solvens
	280	4,44	a
	276	4,44	b
	298	4,54	c
	300	4,59	d
	312,5	4,69	e
	310	4,80	c
	336	4,66	e
	359	4,71	e
	327,5		e

Konjugation befähigt sein. Im Einklang damit findet man in der Reihe der Polyphenyl-oxdiazole mit steigender Zahl der aromatischen Reste eine Rotverschiebung der Absorptionsbanden. Dass die Maxima sogar zahlenmässig denen der Polyphenyle nahekommen, ist überraschend. Das 2,5-disubstituierte 1,3,4-Oxdiazolsystem entspricht somit in der Lichtabsorption der *p*-Phenylen-Einheit.

Die spektrale Ähnlichkeit von 2-Phenyl- und 2,5-Diphenyl-1,3,4-oxdiazol mit Biphenyl und Terphenyl wurde schon in der Mitteil. I beschrieben.[5] Die Fig. 2 illustriert die gleiche Beziehung für die vier- und fünfkernigen Systeme. Die Tabelle 1 bietet die Bandenmaxima mit ihren Extinktionen. Das *p*-Noviphenyl als Gegenstück zum

neunkernigen System X, dessen Lichtabsorption wegen der geringen Löslichkeit nur qualitativ aufgenommen werden konnte, ist unbekannt.

EXPERIMENTELLER TEIL

Versuche zur doppelseitigen Duplikation

Terephthalsäure-dinitril. Terephthalsäure wurde in warmem wässrigen Ammoniak gelöst und zur Trockne eingeengt. Das kristalline Diammonium-terephthalat wurde bei 120–130° bis zur Gewichtskonstanz getrocknet.

Die innig verriebene Mischung von 31·2 g des Diammonium-salzes mit 120 g Phosphorpentoxyd wurde im Schwertkolben im Wasserstrahlvakuum mit freier Flamme erhitzt; unter Verfärbung und Aufblähen verflüssigte sich das Gemisch. Das Sublimat und rasch erstarrende Destillat wurden fein gepulvert und mit warmem wässrigen Ammoniak mehrmals zur Entfernung saurer Anteile digeriert. Das zurückbleibende, bei 218–220° schmelzende Terephthal-dinitril war für die weitere Umsetzung genügend rein (Lit.[12] 223°). Ausbeute: 9·8 g (49% d.Th.).

1,4-*Di*-[*tetrazolyl*-(5)]-*benzol* (V). 42 g Terephthalsäure-dinitril (0·32 Mol) wurden mit 65 g Natriumazid (1·0 Mol) und 42·5 g Lithiumchlorid (1·0 Mol) in 400 cc Glykol-monomethyläther 172 Stdn unter Rückfluss gekocht. Nach Eingiessen in 600 cc Wasser wurde von etwas Ungelöstem abfiltriert und mit 200 cc halbkonz. Salzsäure angesäuert (Abzug!). Das kristalline Rohprodukt wurde abgesaugt, mit Wasser gewaschen und im Vak. über Phosphorpentoxyd getrocknet: 64 g (91% d.Th.) mit Schmp. 296–297° unter Zersetzung. Das reine farblose V zeigte nach Umlösen aus Dimethylformamid den Zersetzungspunkt bei 304° (Lit.[13] >300°). Das IR-Spektrum (KBr-Pressling) bietet im Bereich der NH-Valenzschwingung eine breite, gegliederte Bande, die auf das Nebeneinander verschiedener H-Brückentypen im Kristall weist.[14] Charakteristische Banden liegen bei 705, 734 und 854/cm.

$C_8H_6N_8$ (214·2) Ber. C 44·86 H 2·82
Gef. C 44·71 H 2·99

1,4-*Di*-[2-*phenyl*-1,3,4-*oxdiazolyl*-(5)]-*benzol* (VI). 0·64 g V wurden in 15 cc wasserfreiem Pyridin mit 1·7 cc Benzoylchlorid zum Sieden erhitzt. Innerhalb von einer Stde. wurden 1·98 Moläquival. Stickstoff freigesetzt. Nach Erkalten wurde zur Hydrolyse des Säurechlorids mit einigen Tropfen Wasser versetzt und nach 10 Min. in Wasser eingegossen. Absaugen, Auswaschen und Trocknen führte zu 1·05 g farblosem Produkt mit Schmp. 320·5–322° (96% d.Th.). Aus Dimethylformamid kamen bei 322–322·5° schmelzende Nadeln. (Lit.[15] 308–309°).

$C_{22}H_{14}N_4O_2$ (366·4) Ber. C 72·12 H 3·86 N 15·29
Gef. C 72·31 H 4·05 N 15·03

1,4-*Di*-[2-(p-*nitrophenyl*)-1,3,4-*oxdiazolyl*-(5)]-*benzol* (VII). Bei der analogen Umsetzung von 0·64 g V mit 1·9 g *p*-Nitro-benzoyl-chlorid begann schon in der Siedehitze die Kristallisation des Produkts. Die übliche Aufarbeitung gab 1·34 g VII (98% d.Th.) als blassgelbes Kristallpulver, welches den gleichen Schmp. 405–406° zeigte wie die zarten Blättchen, die beim Umlösen aus siedendem Nitrobenzol erhalten wurden.

$C_{22}H_{12}N_6O_6$ (456·4) Ber. C 57·89 H 2·65
Gef. C 57·57 H 2·71

1,4-*Di*-[2-(p-*cyano-phenyl*)-1,3,4-*oxdiazolyl*-(5)]-*benzol* (VIII). 21·4 g V (100 mMol) wurden mit 33·1 g *p*-Cyan-benzoyl-chlorid[15] (200 mMol, Schmp. 68–70°, Sdp. 143°/20 Torr) in 150 cc wasserfreiem Pyridin rückflussgekocht. Nach 2 Stdn. erreichte die Stickstoff-Freisetzung mit nahezu 5 l den

[12] F. Kaufler, *Ber. Dtsch. Chem. Ges.* **34**, 1577 (1901).
[13] W. G. Finnegan, R. A. Henry und R. Lofquist, *J. Amer. Chem. Soc.* **80**, 3908 (1958).
[14] Vgl. W. Otting, *Chem. Ber.* **89**, 2887 (1956).
[15] J. N. Ashley, H. J. Barber, A. J. Ewins, G. Newbery und A. D. H. Self, *J. Chem. Soc.* 103, 115 (1952) geben Schmp. 65° an.

theoret. Wert. Es wurde in 2 l Wasser eingegossen, abgesaugt, gründlich ausgewaschen und getrocknet: 36·1 g VIII (87% d.Th.). Eine aus Benzonitril umkristallisierte, farblose Probe mit Schmp. 395° wurde analysiert. Die CN-Valenzschwingung findet sich im IR-Spektrum des KBr-Presslings bei 2240/cm. Andere starke Banden bei 712, 743, 857, 966, 1018, 1075, 1110, 1413, 1496 und 1572/cm.

$C_{24}H_{12}N_6O_2$ (416·4) Ber. C 69·22 H 2·91 N 20·18
Gef. C 68·93 H 3·29 N 20·32.

1,4-*Di*-[2-*methyl*-1,3,4-*oxdiazolyl*-(5)]-*benzol*. 0·64 g V entwickelten in 15 cc siedendem Acetanhydrid rasch 2 Äquival. Stickstoff. Beim Erkalten schieden sich farbl. Prismen aus, die abgesaugt und mit Aceton gewaschen wurden: 0·65 g (90% d.Th.) vom Schmp. 261–262°. Umkristallisieren aus Äthanol erhöhte den Schmp. nur unwesentlich auf 262–263°.

$C_{12}H_{10}N_4O_2$ (242·2) Ber. C. 59·50 H 4·17 N 23·13
Gef. C 59·56 H 4·23 N 23·29

1,4-*Di*-{2-(p-[*tetrazolyl*-(5)]-*phenyl*)-1,3,4-*oxdiazolyl*-(5)}-*benzol* (IX). 25·0 g Dinitril VIII wurden mit 14·5 g 80-proz. Lithiumazid in 600 cc Dimethylformamid 240 Stdn. am Rückflusskühler zum Sieden erhitzt. Das Di-tetrazol IX, das sich nach Eingiessen in 2 l Wasser und Ansäuern mit halbkonz. Salzsäure voluminös ausschied, war schwer von Wasser zu befreien: Nach Absaugen und zweimaligem Auskochen mit viel Wasser wurde es bei 150°/15 Torr getrocknet: 27·7 g (92% d.Th.). Das Umkristallisieren gelang durch Hülsenextraktion mit siedendem Pyridin; das farbl. Präparat zersetzte sich gegen 390°. Neben der starken und breiten NH-Bande zeigt das IR-Spektrum (KBr-Pressling) kräftige Banden bei 711, 726, 850, 992, 1074, 1416, 1440, 1486, 1574 und 1640/cm.

$C_{22}H_{14}N_{12}O_2$ (502·5) Ber. C 57·36 H 2·80
Gef. C 56·97 H 3·33.

1,4-*Di*-{2-(p-[2-*phenyl*-1,3,4-*oxdiazolyl*-(5)]-*phenyl*)-1,3,4-*oxdiazolyl*-(5)}-*benzol* (X): Die Suspension von 2·01 g IX in 20 cc siedendem Pyridin reagierte recht glatt mit 1·5 cc Benzoylchlorid. Innerhalb weniger Stdn. wurden 194 cc, d.s. 1·97 Moläquival., Stickstoff entwickelt. Das blassbraungelbe kristalline Produkt (2·38 g entsprechen 91% d.Th.) war in allen Solventien unlöslich und zeigte Zersetzungspunkt gegen 465°. Ein mit Dimethylformamid und mit Pyridin ausgekochtes und sorgfältig getrocknetes Präparat wurde analysiert.

$C_{36}H_{22}N_8O_4$ (654·6) Ber. C 69·72 H 3·39
Gef. C 69·52 H 3·69

Im CH-Wagging-Gebiet des IR-Spektrums gehen die Banden bei 685 und 718/cm vielleicht auf die monosubstituierten, die bei 855/cm auf die disubstituierten Benzolkerne zurück.

Neunkerniges Dinitril XI. Auch bei der Umsetzung von 2·01 g IX mit 1·35 g *p*-Cyan-benzoylchlorid in 20 cc siedendem Pyridin bot die Stickstoffentwicklung ein Mass für den vollständigen Ablauf; die Reaktion vollzog sich in der Suspension. Das zu 80% d.Th. (2·25 g) erhaltene, schwach gefärbte Dinitril war so schwerlöslich, dass das Umkristallisieren scheiterte; die Substanz war nicht analysenrein zu erhalten. Das IR-Spektrum ist frei von NH-Schwingungen; die Nitrilbande liegt bei 2240/cm.

Versuche zur einseitigen Verlängerung der Polyaryl-Kette

2-*Phenyl*-5-[p-*cyano-phenyl*]-1,3,4-*oxdiazol* (XII). Unter den früher beschriebenen Bedingungen[4] brachten wir 3·5 mMol 5-Phenyl-tetrazol mit 5·0 mMol *p*-Cyan-benzoylchlorid zur Reaktion. Das zu 96% d.Th. erhaltene XII kam aus Äthanol in farbl. Nadeln mit Schmp. 191–191·5°. Das IR-Presslingsspektrum zeigt die Nitrilbande bei 2226/cm; die Bandenfolge zunehmender Intensität bei 965, 1018 und 1071/cm findet sich bei allen 2,5-disubstituierten Oxdiazolen. Die CH-Waggingschwingung des *p*-disubstituierten Benzolkerns ist aufgespalten: 856 und 871/cm. Weitere starke Banden liegen bei 685, 708, 739 und 778/cm.

$C_{15}H_9N_3O$ (247·2) Ber. C 72·87 H 3·67
Gef. C 72·62 H 3·67.

1-[2-*Phenyl*-1,3,4-*oxdiazolyl*-(5)]-4-[*tetrazolyl*-(5)]-*benzol* (XIII). 2·49 g XII (10 mMol) wurden mit 1·68 g Natriumazid und 1·22 g Lithiumchlorid in 20 cc Methylglykol 130 Stdn. rückflussgekocht. Die übliche Aufarbeitung gab 2·80 g XIII (97% d.Th.); aus Methanol kristallisierten feine farbl. Nadeln, die bei 268° unter Zersetzung schmelzen.

$C_{15}H_{10}N_8O$ (290·3) Ber. C 62·06 H 3·48 N 28·95
Gef. C 62·00 H 3·60 N 28·70

1,4-*Di*-[2-*phenyl*-1,3,4-*oxdiazolyl*-(5)]-*benzol* (VI). 0·74 g XIII wurden mit 1 cc Benzoylchlorid in 20 ccm Pyridin wie oben umgesetzt (69 cc N_2, 1·08 Moläquival.): 0·89 g VI (95% d.Th.) vom Schmp. 312°. Umlösen aus Dioxan steigerte den Schmp. auf 322°. Mischschmp. und IR-Spektrum erwiesen die Identität mit dem Produkt aus V und 2 Benzoylchlorid (S. 249).

Thermolyse des 4-[*Tetrazolyl*-(5)]-*benzoylchlorids* (XIV)

1·90 g 5-[*p*-Carboxy-phenyl]-tetrazol[5] (10 mMol) wurden mit 10 mMol Thionylchlorid in 20 cc trockenem Xylol 4 Stdn. unter Rückfluss gekocht. Das bis zum Schluss heterogene System wurde im Vak. vom Solvens befreit. Dem hellbraunen Rückstand liessen sich mit siedender 2n Natronlauge 0·84 g des eingesetzten Tetrazolderivats entziehen. Der alkaliunlösliche Anteil (0·89 g) entsprach in der Schwerlöslichkeit der Verbindung X; oberhalb 390° färbt sich das Produkt dunkel und verkohlt, ohne zu schmelzen. Das IR-Spektrum zeigte schwache NH-, OH- und Carbonyl-Absorption; starke Banden bei 720 und 854/cm, schwache Bande bei 794/cm.

Der Deutschen Forschungsgemeinschaft und den European Research Associates (Director Dr. R. H. Gillette), Brüssel, sei für die Förderung der Untersuchung aufrichtig gedankt. Für die Messung der UV-Spektren danken wir Herrn H. Huber an unserem Institut.

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CYCLODEHYDRATION OF DIPHENYL-TRIFLUOROMETHYL-CARBINOLS

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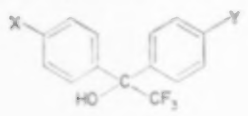
(*Received* 7 *June* 1960)

Abstract—The halochromic product from di-(*p*-fluorophenyl) -trifluoromethylcarbinol and sulphuric acid gives with ethyl mercaptan 3-ethylthio-6 fluoro-9-trifluoromethylfluorene. Analogous reactions have been observed with (*p*-chlorophenyl)-(*p*-fluorophenyl)-, with (*p*-fluorophenyl)-phenyl-, and with diphenyl-trifluoromethyl-carbinol.

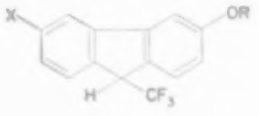
The infra-red spectra of the fluorene derivatives formed are discussed.

DI-(*p*-HALOGENOPHENYL)-TRIFLUOROMETHYL-CARBINOLS (I), when treated successively with concentrated sulphuric acid and water (or methanol) are converted into 3-halogeno-6-hydroxy (or methoxy)-9-trifluoromethylfluorenes (II), by a mechanism which has been discussed previously,[1,2]

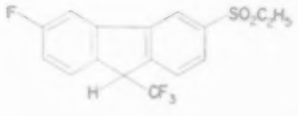
In the present paper an attempt is made to determine the scope of this reaction. (*p*-Chlorophenyl)-(*p*-fluorophenyl)-trifluoromethyl-carbinol, prepared from *p*-chloro-ω,ω,ω-trifluoroacetophenone and *p*-fluorophenylmagnesium bromide, was transformed under the above conditions into 3-chloro-6-methoxy-9-trifluoromethylfluorene (II, X = Cl; R = CH_3); the fluorine atom is thus exchanged in preference to the chlorine atom. (*p*-Fluorophenyl)-phenyl-trifluoromethylcarbinol, prepared analogously from ω,ω,ω-trifluoroactophenone, when treated with sulphuric acid and then with methanol or water, gave 3-methoxy- and 3-hydroxy-9-trifluoromethylfluorene (II, X = H, R = CH_3 or H), respectively; the previously suggested reaction mechanism explains adequately this course of the reaction.



I



II



III

(*o*-Chlorophenyl)-phenyl-trifluoromethyl-carbinol, obtained from ω,ω,ω-trifluoroacetophenone and *o*-chlorophenylmagnesium bromide, gave qualitatively the same picture as the carbinols studied before (strong halochromism, quickly fading in colour); however, no defined product could be obtained upon treatment of the resulting solution with water or methanol.

It is interesting that also the unsubstituted diphenyl-trifluoromethyl-carbinol undergoes a cyclodehydration reaction, when treated with concentrated sulphuric acid. According to its analysis and spectrum, the product, obtained in low yield, is 9-trifluoromethylfluorene. This reaction is analogous to the conversion of benzilic to fluorene-9-carboxylic acid.[3]

[1] S. Cohen, *J. Amer. Chem. Soc.* **79**, 1499 (1957).
[2] S. Cohen and A. Kaluszyner, *Experientia* **13**, 236 (1957).
[3] D. Vorlaender, *Ber. Dtsch. Chem. Ges.* **44**, 2467 (1911).

The product formed from di-(*p*-fluorophenyl)-trifluoromethyl-carbinol and sulphuric acid underwent with *ethyl mercaptan* a reaction analogous to that occurring with water or alcohols. Although the expected 3-ethylthio-6-fluoro-9-trifluoromethyl-fluorene could not be induced to crystallize, the corresponding sulphone (III), formed from the crude reaction product with hydrogen peroxide, was well-defined and gave correct analytical figures.

The previously described[4] di-(*p*-chlorophenyl)-pentafluoroethyl- and -heptafluoropropyl-carbinols behave exactly like the corresponding trifluoromethyl compound. Successive treatment with sulphuric acid and methanol gave two compounds which according to their analyses and spectra, were 3-chloro-6-methoxy-9-pentafluoroethyl- and -9- heptafluoropropyl-fluorene, respectively.

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The structure of the products obtained in the cyclodehydration reactions was deduced from the infra-red and ultra-violet spectra. The latter resemble closely that of fluorene derivatives.[1,2] It was found that the compounds II (R = CH_3, X = H or Cl) showed an infra-red C—H frequency at about 3400 cm^{-1}. It is suggested that this frequency is due to the C—H bond in the 9-position. Acetylene, too, has an unusually high C—H frequency (3270–3305 cm^{-1}).[5] Experiments of our own have shown that fluorene has a peak at 3330 cm^{-1}, and methyl fluorene-9-carboxylate, which is structurally similar to II, at 3400 cm^{-1}; 9,9-diphenylfluorene, which lacks a hydrogen atom in the 9-position, has no band beyond 3000 cm^{-1}.[6]

EXPERIMENTAL

(p-*Chlorophenyl*)-(p-*fluorophenyl*)-*trifluoromethyl-carbinol* (I, X=Cl, Y=F). To a Grignard solution prepared from magnesium (2·45 g) and *p*-fluorobromobenzene (17·5 g) in ether (150 cc), dry toluene (100 cc) was added and the ether distilled off. Then *p*-chloro-ω,ω,ω-trifluoroacetophenone[4] (10·4 g) was added dropwise and with stirring to the hot mixture (80–90°) over a period of 20 min. Refluxing was continued for an additional 30 min, then the mixture was cooled, decomposed with ice and sulphuric acid and extracted with ether. Distillation of the ethereal layer yielded the desired *compound* as a yellowish oil, b.p. 131–135°/2 mm. Yield, 12·5 g (82%); n_D^{25} 1·5301, d_{25}^{25} 1·395. MR, Found: 67·54; MR, Calc.: 67·35. $\tilde{\nu}_{max}^{liq}$: 3550 (hydroxyl), 1165 (CF_3), 1068 (C—F), 752 (C—Cl) cm^{-1}. (Found: C, 55·6; H, 3·2. $C_{14}H_8ClF_4O$ requires: C, 55·2; H, 3·0%).

3-*Chloro*-6-*methoxy*-9-*trifluoromethylfluorene* (II, X = Cl, R = CH_3). A mixture of the foregoing carbinol (2·8 g) and conc sulphuric acid (20 cc) was shaken for 3 hr, kept overnight, and the coloured solution added, dropwise and with stirring, to an excess of methanol at 5–10°. Crushed ice was added and the precipitated material collected and recrystallized from methanol (charcoal) to yield 1 g (36%) of 3-*chloro*-6-*methoxy*-9-*trifluoromethylfluorene*, m.p. 97–99° (lit:[1,2] 95–96°). No depression was observed in the m.p. of a mixture of this compound with an authentic sample. λ_{max}^{EtOH} 217 (4·39); 240 (4·21); 302 (3·70); 308 (3·74); 310 mμ (3·85). $\tilde{\nu}_{max}^{KBr}$ 3420 (C_9—H), 1265 (Ar—O—CH_3), 1165 (CF_3), 1038 (C—F), 744 (C—Cl) cm^{-1} (Found: C, 60·7; H, 3·5; F, 19·3%. Calc. for $C_{15}H_{10}ClF_3O$: C, 60·3; H, 3·4; F, 19·1%).

(p-*Fluorophenyl*)-*phenyl*-*trifluoromethyl-carbinol* (I, X = H, Y = F). To a solution of the Grignard reagent, prepared from magnesium (2·4 g), and *p*-fluorobromobenzene (17·5 g) in ether (150 cc), a solution of ω,ω,ω-trifluoroacetophenone[7] (15 g) in ether (75 cc) was added dropwise and with stirring over a period of 15 min, so that the mass was kept boiling. It was then refluxed for 15 min, cooled and poured into a mixture of crushed ice and sulphuric acid. The organic layer was separated, and the aqueous layer extracted once with ether. The combined ether extracts were dried over sodium sulphate and distilled. The *carbinol* forms a colourless oil of b.p. 120–125°/3 mm. Yield, 15 g (71%).

[4] A. Kaluszyner, S. Reuter and E. D. Bergmann, *J. Amer. Chem. Soc.* 77, 4164 (1955).
[5] R. N. Jones and C. Sandorfy, *Chemical Applications of Spectroscopy* p. 387. Interscience, New York (1956).
[6] G. W. H. Scherf and R. K. Brown, *Canad. J. Chem.* **38**, 697 (1960).
[7] A. Sykes, J. C. Tatlow and C. R. Thomas, *Chem. & Ind.* 630 (1955).

n_D^{25} 1·5180; d_{25}^{25} 1·331. MR, Found: 61·46; MR, calc.: 61·82. $\tilde{\nu}_{max}^{liq.}$ 3450 (hydroxyl), 1163 (CF_3), 1065 (C—F) cm^{-1}. (Found: C, 62·6; H, 4·1. $C_{14}H_{10}F_4O$ requires: C, 62·2; H, 3·7%).

The *acetate* was prepared by heating for 3 hr at 100° a mixture of the carbinol (0·5 g), acetic anhydride (4 cc) and sulphuric acid (2 drops), decomposition with ice and recrystallization of the organic product from methanol. M.p. 70–71°. $\tilde{\nu}_{max}^{KBr}$ 1770 (carbonyl), 1175 (CF_3), 1024 (C—F) cm^{-1}. (Found: C, 61·7; H, 4·3. $C_{16}H_{12}F_4O_2$ requires: C, 61·5; H, 3·9%).

3-*Methoxy*-9-*trifluoromethylfluorene* (II, X = H, R = CH_3). A mixture of the foregoing carbinol (1 g) and conc sulphuric acid (20 cc) was shaken for 1 hr and the coloured solution added, dropwise and with stirring, to an excess of methanol at 5–10°. Crushed ice was added, whereupon crystals of 3-*methoxy*-9-*trifluoromethylfluorene* separated. The compound was purified by recrystallization from methanol or petroleum ether and formed silky needles of m.p. 87–88°. Yield, 0·6 g (61%). $\tilde{\nu}_{max}^{KBr}$ 3400 (C_s—H), 1235 (Ar—O—CH_3) 1165 (CF_3), 1038 (C—F) cm^{-1}. λ_{max}^{EtOH} 213 (4·43); 235 (4·31); 262 (4·14); 270 (4·15); 288 (3·50); 298 (3·62); 303 (3·64); 310 mμ (3·85) (Found: C, 68·3; H, 4·3. $C_{15}H_{11}F_3O$ requires: C, 68·2; H, 4·2%).

3-*Hydroxy*-9-*trifluoromethylfluorene* (II, X = R = H). The product from the carbinol (I, X = H, Y = F) and conc sulphuric acid (20 cc) was poured onto crushed ice. The compound was extracted with ether and the ether residue recrystallized from carbon tetrachloride to yield 0·3 g (32%) of the *compound*, m.p. 174–176°. $\tilde{\nu}_{max}^{KBr}$ 3280 [hydroxyl and C_s—H(?)], 1165 (CF_3) cm^{-1}. λ_{max}^{EtOH} 213 (4·34); 236 (4·26); 263 (4·14); 270 (4·15); 290 (3·45); 305 (3·65); 312 mμ (3·73). (Found: C, 66·8; H, 3·7; F, 22·3. $C_{14}H_9F_3O$ requires: C, 67·2; H, 3·6; F, 22·8%).

(*o*-*Chlorophenyl*)-*phenyl*-*trifluoromethyl*-*carbinol*. To a solution of the Grignard reagent, prepared from magnesium (2·9 g) and *o*-bromochlorobenzene (23 g) in ether (100 cc), dry toluene (70 cc) was added and the ether removed. Then a solution of ω,ω,ω-trifluoroacetophenone (17·4 g) in toluene (40 cc) was added with stirring, at the b.p. of the mixture, over a period of 20 min; refluxing was further maintained for 30 min. After decomposition with ice and sulphuric acid, separation of the ethereal layer and distillation, the *carbinol* was obtained as a yellowish oil, b.p. 139–141°/2 mm; yield, 9 g (31%). $\tilde{\nu}_{max}^{liq.}$ 3580 (hydroxyl), 1165 (CF_3); 1040 (C—F); 752 (C—Cl) cm^{-1}. (Found: F, 19·7. $C_{14}H_{10}ClF_3O$ requires: F, 19·9%).

The *acetate* prepared from the carbinol, acetic anhydride and sulphuric acid, melted at 45–47°. (Found: C, 58·3; H, 3·5. $C_{16}H_{12}ClF_3O_2$ requires: C, 58·5; H, 3·7%).

The carbinol (3 g) and conc sulphuric acid (20 cc) gave a deep-purple solution; the colour changed within a few minutes to a dirty green. No defined material could be obtained by either treating this product with crushed ice or cold methanol.

9-*Trifluoromethylfluorene*. Conc sulphuric acid (60 g) was added in portions to powdered diphenyl-trifluoromethyl-carbinol[4] (10 g) in a mortar and the mass triturated till the red-brown colour did no longer appear. The grey mass was then added to an excess of ice and the precipitate filtered off and dried to yield 9·7 g of m.p. 58–100°. The product was extracted with hot methanol; from the filtered solution separated, upon concentration, 9-*trifluoromethylfluorene* which was purified by recrystallization from glacial acetic acid; yield, 0·7 g (7·5%), m.p. 170·5–171°. λ_{max}^{EtOH} 235 mμ (3·90); 271 mμ (3·90); 294 mμ (3·23); 306 mμ (3·16). (Found: C, 71·8; H, 4·0; F, 24·5. $C_{14}H_9F_3$ requires: C, 71·8; H, 3·9; F, 24·3%).

3-*Chloro*-6-*methoxy*-9-*pentafluoroethyl*-*fluorene*. A mixture of di-(*p*-chlorophenyl)-pentafluoroethyl-carbinol[4] (7·4 g) and conc sulphuric acid (60 cc) was shaken mechanically for 3 hr, allowed to stand overnight and added, dropwise and with stirring, to methanol (200 cc) at 5–10°. The methanolic solution was poured onto crushed ice and the *product* recrystallized from petroleum ether (b.p. 60–90°), m.p. 89–91°; yield, 2·1 g (30%). λ_{max}^{EtOH} 218 mμ (4·66); 238 mμ (4·48); 265 mμ (4·24); 292 mμ (3·75); 302 mμ (3·85); 314 mμ (3·98). (Found: C, 55·3; H, 3·1. $C_{16}H_{10}ClF_5O$ requires: C, 55·1; H, 2·9%).

3-*Chloro*-6-*methoxy*-9-*heptafluoropropyl*-*fluorene*. This compound was obtained from di-(*p*-chlorophenyl)-heptafluoropropyl-carbinol[4] (8·4 g) and conc sulphuric acid (60 cc), as described above. Yield, 2·2 g (27%), m.p. 84–85·5° (from pet ether b.p. 60–90°). λ_{max}^{EtOH} 240 mμ (4·32); 266 mμ (4·00); 273 mμ (4·00); 314 mμ (3·88). (Found: C, 51·2; H, 2·8. $C_{17}H_{10}ClF_7O$ requires: C, 51·2; H, 2·5%).

3-*Ethylsulphonyl*-6-*fluoro*-9-*trifluoromethylfluorene* (III). A mixture of di-(*p*-fluorophenyl)-trifluoromethyl-carbinol (2·9 g) and conc sulphuric acid (30 cc) was shaken mechanically for 3 hr, then added, dropwise and with stirring, to ethyl mercaptan (100 g) at 0°. The colour of the first drops faded

quickly, but soon a second layer was formed, and vigorous stirring was required to bring about this change. The mixture was added to excess cold water, the organic layer separated and subjected to distillation, first at atmospheric pressure, then *in vacuo* in order to remove some diethyl disulphide. The residual oil could not be induced to crystallize; it was dissolved in glacial acetic acid (20 cc) and oxidized to the sulphone with 30% hydrogen peroxide (5 cc) on the water bath for 30 min. After 12 hr. at room temp, the solution was diluted with water and neutralized partially with sodium bicarbonate, whereupon crystals of *3-ethylsulphonyl-6-fluoro-9-trifluoromethylfluorene* (III) separated; yield, 1·1 g (32%). They were purified by recrystallization from a petroleum ether–chloroform mixture and subsequently from ether; b.p. 137–138·5°. (Found: C, 55·6; H, 3·4. $C_{16}H_{12}F_4O_2S$ requires: C, 55·8; H, 3·5%).

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NAPHTHAQUINONES—II

DERIVATIVES OF NAPHTHALENE-2,7-DIOL

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Abstract—The oxidation of 1,6-dibromo-2,7-dimethoxynaphthalene has been reinvestigated and the 1-bromodimethoxy-compound has yielded a new bromonaphthaquinone. A transbromination of 1,6-dibromonaphthalene-2,7-diol has been noticed, whilst an azo-dye from this dibromodiol is shown to have a structure different from that expected from the earlier literature.

As a sequel to recent work[1] the present paper concerns investigations relating mainly to the structures of the chief products of mono- and di-bromination of naphthalene-2,7-diol.

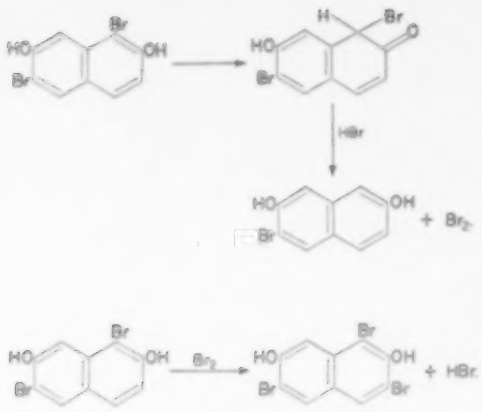
Cooke *et al.*[2] have prepared, for the first time, pure 1,6-dibromonaphthalene-2,7-diol and have indicated that the 1,8-dibromo-compound can be converted into the apparently more stable 1,6-dibromodiol by heating in hydrobromic acid in acetic acid. Full details of their methods do not appear to have been published,* but the present author has prepared pure 1,6-dibromonaphthalene-2,7-diol by chromatography on alumina. It seemed likely† that the crude product of attempted dibromination of naphthalene-2,7-diol consisted of mainly the 1,6- and 1,8-dibromo-derivatives. Thus treatment of this product with hydrobromic acid in acetic acid was expected to give a better yield of the 1,6-dibromo-compound by isomerization of the 1,8-dibromo-derivative in the mixture.[3] With hydrogen bromide in aqueous acetic acid an intermolecular change seemed to occur, since the only isolated compound was the 1,3,6-tribromodiol. To ensure that this result did not arise merely from the presence of the tribromo-compound in the starting material, a similar experiment was conducted on pure 1,6-dibromodiol. The only pure product obtained in this case, as also when water was omitted, was the tribromodiol. It appears, then, that, in the preparation of 1,6-dibromonaphthalene-2,7-diol by direct bromination, it is inadvisable to heat the reaction-mixture, since production of the tribromo-derivative may ensue in the medium containing hydrogen bromide as a product of the initial bromination.

The mechanism of this transbromination is presumably as indicated below.[4] Steric hindrance to substitution in the 8-position of the 1,6-dibromodiol would make the

* The work of R. G. Cooke, B. L. Johnson and W. R. Owen has now been published in detail [*Austral. J. Chem.* **13**, 256 (1960)]. They have given evidence that the compound, which was earlier[2] thought to be the 1,8-dibromo-diol, is the 1,3-isomer.

† See Ref. 2 and analytical results of Ref. 3.

[1] R. D. Wilson, *Tetrahedron* **3**, 236 (1958).
[2] R. G. Cooke, B. L. Johnson and W. R. Owen, *Chem. & Ind.* 1623 (1957).
[3] I. S. Ioffe and N. M. Fedorova, *Zh. Obshchei Khim.* **6**, 1079 (1936); *Chem. Abstr.* **31**, 1022 (1937).
[4] R. H. Thomson, *Quart. Rev.* **10**, 32 (1956); P. B. D. de la Mare and J. H. Ridd, *Aromatic Substitution: Nitration and Halogenation* p. 123. Butterworths, London (1959); P. W. Robertson, *J. Chem. Soc.* 1883 (1956); H. Franzen and G. Stäuble, *J. Prakt. Chem.* **103**, 352 (1922); E. S. Lewis and M. C. R. Symons, *Quart. Rev.* **12**, 242 (1958).



1,3,6-tribromo-compound the main product of further bromination.[5] Regarding the structure of the tribromo-derivative, Cooke *et al.*[2] have made 3,6-dibromonaphthalene-2,7-diol by the reduction of the product of brominating naphthalene-2,7-diol with three moles of bromine per mole of the diol.* In view of the reduction of the 1,8-dibromodiol to the 3-bromodiol,[2] it is possible that reducing 1,3,8-tribromonaphthalene-2,7-diol would give the 3,6-dibromo-compound.

Ethylation of the 1,6-dibromodiol afforded crude material melting at about 85°. In preliminary work some difficulty was encountered in trying to obtain a pure compound, analyses indicating incomplete ethylation.

Methylation of the dichloronaphthalene-2,7-diol has been shown to give a product identical with that from the chlorination of 2,7-dimethoxynaphthalene.[1] Thus it is confirmed that naphthalene-2,7-diol and its dimethyl ether yield similarly orientated main products on direct dichlorination (cf. dibromination[6]).

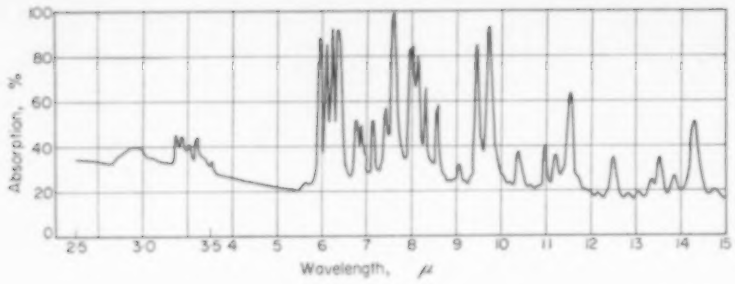
Naphthaquinones

2,6- and 2,7-Dimethoxynaphthalenes were separately treated with chromic acid. By chromatography 2,7-dimethoxy-1,4-naphthaquinone has been prepared in a purer state than heretofore.[1,7] No pure compound was isolated from this oxidation of 2,6-dimethoxynaphthalene, but the use of a different oxidant† yielded the expected quinone as one of the products.

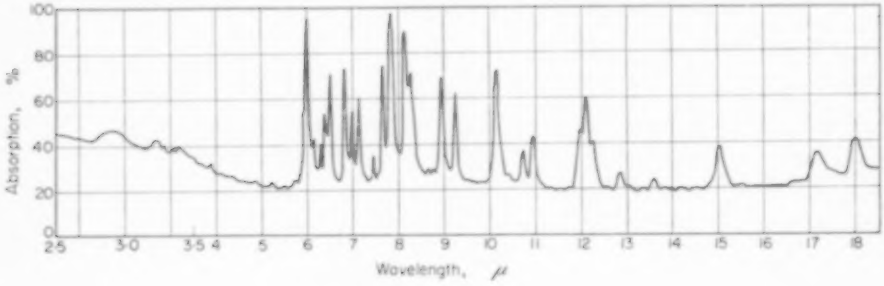
Oxidation of the product of direct monobromination of 2,7-dimethoxynaphthalene has, despite the use of chromatography, afforded only a bromo-2,7-dimethoxy-1,4-naphthaquinone, which is concluded to have the structure (I). Assigning this formula (5-bromo-3,6-dimethoxy-1,4-naphthaquinone) is compatible with the results of, first, the oxidation of 1,6-dibromo-2,7-dimethoxynaphthalene and, secondly, the bromination of 2,7-dimethoxy-1,4-naphthaquinone,[1,8] in which 6-bromo- (II) and 3-bromo-2,7-dimethoxy-1,4-naphthaquinone (III) were prepared. It is to be noted that these

* See Ref. 1 on the result of the oxidation of 1,3,6-tribromo-2,7-dimethoxynaphthalene.
† Forthcoming paper.

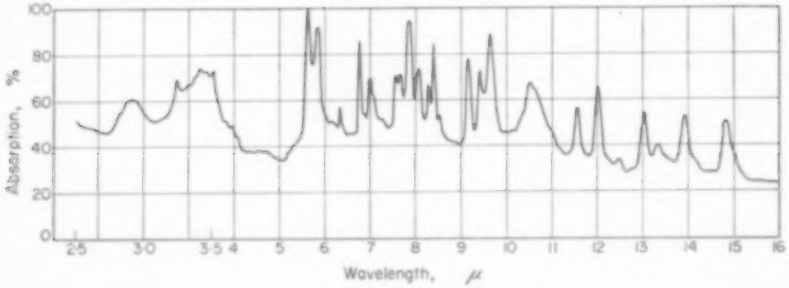
[5] P. B. D. de la Mare and J. H. Ridd, *Aromatic Substitution: Nitration and Halogenation* p. 180. Butterworths, London (1959).
[6] F. Bell, J. A. Gibson and R. D. Wilson, *J. Chem. Soc.* 2335 (1956).
[7] L. F. Fieser and R. H. Brown, *J. Amer. Chem. Soc.* **71**, 3615 (1949).
[8] P. B. D. de la Mare and J. H. Ridd, *Aromatic Substitution: Nitration and Halogenation* p. 185. Butterworths, London (1959).



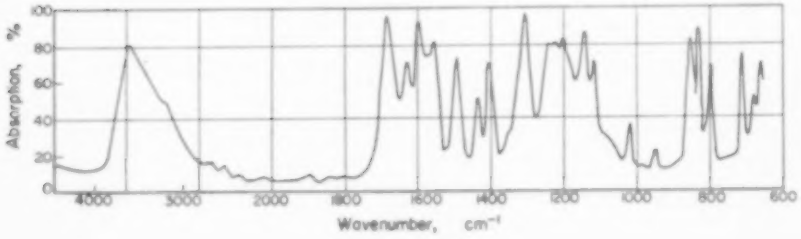
SPECTROGRAM 1.



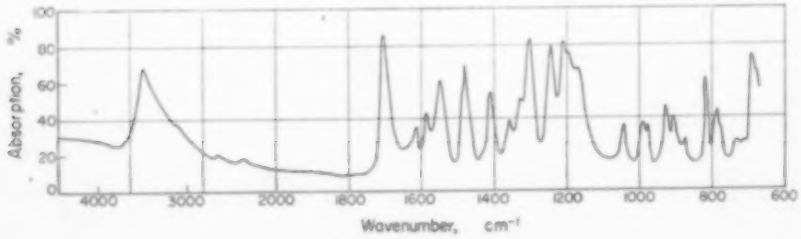
SPECTROGRAM 2.



SPECTROGRAM 3.



SPECTROGRAM 4.

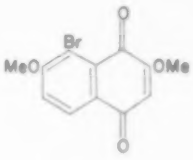


SPECTROGRAM 5.

Number of spectrogram*	Name of compound	Percentage of compound in KBr	Thickness of disk (mm)
1	6-Bromo-2,7-dimethoxy-1,4-naphthaquinone	1	0·3
2	3,8-Dibromo-7-methoxy-1,2-naphthaquinone	1	0·3
3	5-Bromo-2-carboxy-4-methoxyphenylglyoxal	1	0·3
4	1,1,6-Trichloro-1,2-dihydro-7-hydroxy-2-oxonaphthalene	0·5	0·8
5	3,8-Dibromo-1,1,6-trichloro-1,2-dihydro-7-hydroxy-2-oxonaphthalene	0·5	1·0

* The spectra were obtained with a Grubb–Parsons double-beam spectrometer, using a KBr disk.

two compounds would be the only likely significant quinones from the oxidation of the product of monobromination of the dimethoxynaphthalene, if the claim of Ioffe and Fedorova, that monobromination of the 2,7-diol gave the 3-bromo-derivative, were correct.[3]



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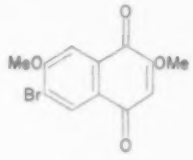
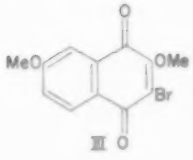


II



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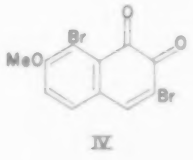

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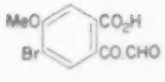
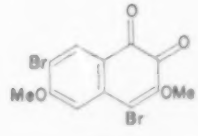


V



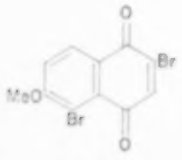
VI

The oxidation of 1,6-dibromo-2,7-dimethoxynaphthalene[1] has been repeated, and it has been possible to isolate purer specimens of the quinones (II, IV) and also an acid (V). The structure (VI) was previously[1] attributed to the 1,2-quinone (cf. the conversion of 1-tetralone into 1,2-naphthaquinone[9]). The determination of the contents of bromine, oxygen and methoxyl group now shows this to be incorrect. It is

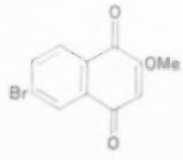
[9] T. Shoji, *J. Pharm. Soc. Japan* **79**, 1034 (1959).

interesting that, while the monobromodimethoxynaphthalene yields, on oxidation, the quinone with the bromine atom retained in the α-position, the dibromo-ether gives the 1,4-quinone with the α-bromine atom removed by the formation of a carbonyl group (cf. the oxidation of the dichloro-ether[1]). The latter result may be related to the inductive deactivation, by the 6-bromo-substituent, to electrophilic attack by the oxidant.[10] From the oxidation of 1,6-dibromo-2-methoxynaphthalene,[6] however, both 1,4-quinones (VII, VIII) were obtained. It is possible that the 7-methoxy-substituent in 1,6-dibromo-2,7-dimethoxynaphthalene impedes sterically the lateral displacement of the 6-bromine atom that may be necessary for the attack in the 5-position by the oxidant. The formation of the 1,2-quinone (IV) by removing the 7-methoxy-group from the dibromodimethoxynaphthalene then appears to be the preferred mode of oxidation of the ring bearing this methoxy-substituent. In the oxidation of 1,3,6-tribromo-2,7-dimethoxynaphthalene[1], in which the steric situation is even more congested, the α-bromine atom is displaced.

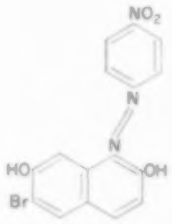
The microanalyses of the acidic product suggest an aldehydic and ketonic monocarboxylic acid. The spectrogram (3), showing strong bands at wavelengths of 5·6, 5·8 and 7·8 μ, is compatible with this.[11] The oxidation of the dibromo-ether seems likely, from the foregoing discussion, to involve preferential attack on the ring with the α-bromo-substituent. The bands at 11·5 and 12·0 μ suggest 1,2,4,5-tetrasubstitution as opposed to the possible 1,2,3,4-tetrasubstitution[12] in the acid, which would arise from rupture of the ring bearing the β-bromo-substituent. Under the influence of the methoxyl group the opening of the ring is then expected to occur between the 1- and 2-carbon atoms. A possible intermediate is an *o*-carboxycinnamic acid, which, on further oxidation, might give the compound V.



VII



VIII



IX

Coupling with diols

So far no success has attended efforts to identify, by reduction, the dyes prepared by coupling *p*-nitrobenzenediazonium chloride with 1-bromonaphthalene-2,7-diol and with the 1,6-dibromodiol. The products of coupling themselves appeared to be impure*, but in one case, from the reaction of 1,6-dibromonaphthalene-2,7-diol with the diazonium chloride, the analytical results suggest that the compound IX was formed. The coupling involving the displacement of the bromo-substituent (as in the

* Cf. Ref. 3.

[10] W. A. Waters, *Quart. Rev.* **12**, 290 (1958); I. Necsoiu and C. D. Nenitzescu, *Chem. & Ind.* 377 (1960).
[11] E. Bernatek, *Tetrahedron* **4**, 216 (1958).
[12] L. J. Bellamy, *The Infrared Spectra of Complex Molecules* (2nd Ed.). Methuen, London (1958); A. D. Cross, *Introduction to Practical Infrared Spectroscopy*. Butterworths, London (1960).

coupling of 1-bromo-2-naphthol[13,14]) thus appears to occur to a significant extent despite the presence of the unsubstituted 8-position in the dibromodiol.

Ioffe and Fedorova[3] considered that the dibromodiol gave a bisazo-dye containing two atoms of bromine in the molecule. This result might be accounted for by the displacement of the α-bromo-substituent as hypobromous acid,[15] which, in the absence of thiosulphate, rebrominated the dye in the available 3-position. The product of such a reaction in an alkaline medium[16] would be, after acidification, 3,6-dibromo-1,8-bis-*p*-nitrobenzeneazonaphthalene-2,7-diol. In relation to this work the effect of thiosulphate on the yield of the bromine-free dye from the coupling of diazotized *p*-nitroaniline with 1-bromo-2-naphthol[15] is emphasized.

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EXPERIMENTAL*

Purification of 1,6-*dibromonaphthalene*-2,7-*diol*

Crude dibromodiol (199 g; m.p. 152·5–153°) was prepared as previously[17] from naphthalene-2,7-diol (101 g). Recrystallization from benzene, *o*-dichlorobenzene, or aqueous acetic acid (5 vols acetic acid : 2 vols water) seemed unpromising (cf. Ref. 3).

Some (5·38 g) of the product (m.p. 152·5–154·5°) of recrystallizing twice from benzene gave, with a mixture of benzene (106 ml) and chloroform (74 ml), a solution which was chromatographed on a column of alumina (46 cm high × 3·2 cm in diameter; column produced from a dispersion of alumina in benzene). Development with benzene produced a narrow, light brownish-grey band above a light cream-coloured band involving the remainder of the column. The latter band was divided into 3 equal portions, each of which was extracted with hot acetic acid. The solvent was removed from the extracts, and the residues were treated separately with hot acetic acid and decolourizing charcoal. Hot filtration was followed by dilution with water, to give precipitates which were filtered off. Recrystallization of the product (c) from a solution of acetic acid (2 vol) in water (1 vol) and then from glacial

Precipitate	W	m.p.
(a) From top third of band	0·85 g	142–148°
(b) From middle third of band	0·89 g	145–148·5°
(c) From lowest third of band	2·04 g	155·5–158°

acetic acid afforded minute white needles (0·55 g) of 1,6-dibromonaphthalene-2,7-diol, m.p. 163–163·5° with sublimation. (Found: C, 38·0; H, 1·9; Br, 50·6. Calc. for $C_{10}H_6Br_2O_2$: C, 37·8; H, 1·9; Br, 50·3%). Crystallization (from benzene; cf. ref. 3) of a specimen melting at 162–162·5° gave a product with m.p. 162·5–163°.

Transbromination

(1) 1,6-Dibromonaphthalene-2,7-diol (0·55 g; m.p. 163–163·5), acetic acid (2·8 ml) and hydrobromic acid (1·4 ml; 48–50% w/w HBr; less than 0·01% w/v Br_2) were heated by a water-bath for 4 hr. The cold product was filtered (filtrate A), and the residue was washed with acetic acid (filtrate B), leaving a solid (0·20 g; m.p. 185·5–195·5°), which was extracted with boiling water. The aqueous

* M.ps are corrected. Most of the microanalyses were carried out through Dr. A. Bernhardt, Mülheim, Germany.

[13] V. Veselý and F. Šturša, *Chem. Listy* **27**, 126 (1933); *Chem. Abstr.* **27**, 5320 (1933).
[14] J. T. Hewitt and H. V. Mitchell, *J. Chem. Soc.* **89**, 1167 (1906).
[15] I. S. Ioffe, *Zh. Obshchei Khim.* **6**, 1074 (1936); *Chem. Abstr.* **31**, 1021 (1937).
[16] P. B. D. de la Mare and J. H. Ridd, *Aromatic Substitution: Nitration and Halogenation* p. 114. Butterworths, London (1959); E. Šilov and N. Kaniaev, *Dokl. Akad. Nauk SSSR* **24**, 890 (1939).
[17] R. D. Wilson, Thesis for the Fellowship of the Heriot-Watt College, Edinburgh (1957).

extract was cooled and filtered, to give about 1 mg of residue, m.p. about 149°, and a filtrate which yielded only a trace of solid on removal of the solvent.

The solid left after extraction by boiling water melted at 190·5–196·5°. Repeated crystallization from acetic acid afforded minute white needles of 1,3,6-tribromonaphthalene-2,7-diol, m.p. 207–208·5° with sublimation. (Found: C, 30·3, 30·5; H, 1·6, 1·3; Br, 60·1. Calc. for $C_{10}H_5Br_3O_2$: C, 30·3; H, 1·3; Br, 60·4%).

The combined filtrates (A) and (B) were diluted to 25 ml with water. Filtration yielded a residue (C) and a solution, which, by removal of the solvent, gave 0·09 g of material, most of which was dissolved by warm chloroform. Removal of chloroform from the solution afforded only an unpromising substance.

The residue (C; 0·19 g; m.p. 142–143°) in toluene was chromatographed on alumina. Toluene was used for development. Removal of solvent from the eluate gave no residue. The column showed four bands, which were extruded. The narrow brownish-grey top band was discarded, whilst the others were extracted separately with hot acetic acid, the latter being subsequently removed from the extracts at 70–100°. The products from the second and third bands (in relation to top of column) were treated individually with 95% ethanol and charcoal. Removal of the charcoal and then the solvent gave impure materials. The product from the fourth band (light grey-blue) was treated with hot 95% ethanol (charcoal). Filtration and addition of water to the filtrate afforded a light grey solid (0·04 g; m.p. 154·5–156°), probably impure dibromodiol.

(2) Impure dibromodiol (7·85 g; m.p. 151·5–153·5°), by heating for 1 hr under similar conditions, gave a residue (D; 2·30 g; m.p. 179–183°) and a filtrate, which was diluted to 500 ml with water, to afford a precipitate (E; 4·36 g; m.p. 145–146°). The m.p. of a mixture of D and E in the proportions in which they had been yielded (28 mg : 53 mg) was 142·5–145·5°. Repeated crystallization (charcoal) of D from acetic acid afforded material m.p. 201·5–203·5° (mixed m.p. with tribromo-compound, m.p. 196·5–198°, made by direct bromination of the 2,7-diol[17] was 199–200·5°). A further crystallization from acetic acid gave minute white needles, 0·47 g; m.p. 205·5–206·5°. (Found: C, 30·8; H, 1·5%). Repeated crystallization (charcoal) of E from acetic acid gave a product, 1·01 g; m.p. 155·5–157°.

(3) Impure dibromodiol (7·85 g; m.p. 151·5–153·5°), acetic acid (25 ml) and a solution of hydrogen bromide in acetic acid (30 ml; 50% w/v HBr; less than 0·1% w/v Br_2) were heated (reflux condenser with $CaBr_2$) in a bath at 100° for 1 hr. The cold product was filtered, to give only a trace of residue. The filtrate was diluted with water to 250 ml, and the resulting precipitate was filtered off and washed with water. The product (5·5 g; m.p. 136·5–140·5°) was crystallized twice from benzene (charcoal), giving a substance (1·1 g) m.p. 165–178°. Repeated crystallization from acetic acid (charcoal) yielded a solid (0·06 g; m.p. 206–208°). Mixed m.p. with tribromonaphthalenediol (m.p. 207–208·5°; as mentioned in section (1) under "Transbromination") was 207–208·5°.

1,6-*Dibromo*-2,7-*diethoxynaphthalene*

A mixture of impure 1,6-dibromonaphthalene-2,7-diol (8·2 g; m.p. 151·5–153·5°) dissolved in acetone ("AnalaR"; 80 ml), potassium carbonate ("AnalaR"; 6·5 g) and diethyl sulphate (9·3 ml) was refluxed for 30 min. The product was concentrated by removal of distillate (40 ml), diluted with water to 250 ml, and then maintained at 40° for 2 hr. Addition of 2 N NaOH (60 ml) preceded further heating at 40° for 1 hr. Filtration and washing of the residue with water afforded a solid (7·1 g), m.p. 77° to above 86°, which was treated with boiling 95% ethanol and charcoal before hot filtration (filtrate F). The residue was agitated with boiling acetic acid and filtered, to leave white crystals (0·26 g; m.p. 154–155·5°; insoluble in boiling 2 N NaOH). Recrystallization from acetic acid gave 1,6-*dibromo*-2,7-*diethoxynaphthalene* as white plates, m.p. 154·5–155·5° and mixed m.p. with pure dibromodiol 135–147° (Found: C, 45·3; H, 3·8; Br, 43·0; EtO, 24·0. $C_{14}H_{14}Br_2O_2$ requires: C, 44·9; H, 3·8; Br, 42·7; EtO, 24·1%).

The filtrate (F) yielded, on cooling, a solid, which, by crystallization from 95% ethanol and then *o*-xylene (charcoal), afforded a product (0·35 g) with a melting range around 145°.

The solvent was removed at reduced pressure from the mother-liquor from the last crystallization. The residue was recrystallized from 95% ethanol, to give a solid (2·5 g), m.p. 81–91°. Chromatography, on cellulose powder, of a solution in benzene/chloroform and, on alumina, of a solution in benzene did not achieve the isolation of a pure compound. Analyses (in particular, for ethoxyl group) suggested mixtures of mono- and di-ethyl ethers of the dibromodiol.

1,6-Dichloro-2,7-dimethoxynaphthalene

1,6-Dichloronaphthalene-2,7-diol (designated earlier[6] as "1,8-dichloro-2,7-dihydroxynaphthalene") was prepared by the reduction, with zinc and acetic acid, of 1,1,6-trichloro-1,2-dihydro-7-hydroxy-2-oxonaphthalene,[17] previously[6] thought to be the 1,1,8-trichloro-compound (spectrogram (4); the spectrogram (5) of a related dibromotrichloro-compound is also shown). Methylation of the dichlorodiol (0·17 g) with dimethyl sulphate in aqueous sodium hydroxide gave a product (0·10 g), m.p. 142°. By recrystallization from acetic acid (charcoal) were obtained prisms, m.p. 143° and mixed m.p. with the product[1] of dichlorination of 2,7-dimethoxynaphthalene 142·5–143·5°.

2,7-Dimethoxy-1,4-naphthaquinone

2,7-Dimethoxynaphthalene (9·34 g) was oxidized as previously.[1] The resulting mixture was diluted with water (400 ml) and extracted repeatedly with 1,2-dichloroethane, the last extract being colourless. The solvent was removed from the extract after drying (Na_2SO_4), to give a solid (3·92 g) A solution of this in chloroform (100 ml) was chromatographed on alumina. Development by chloroform yielded five small brown bands at the top of the column and, at the bottom, a broad yellow band, which was eluted. Removal of the solvent from the eluate gave an orange-yellow solid (1·75 g), m.p. 211–222°. The product of recrystallization from acetic acid was washed with aqueous sodium hydrogen carbonate and then with water. The resultant yellow prisms (1·46 g) melted at 215–216° with sublimation. A mixed m.p. of 214·5–216° was obtained with 2,7-dimethoxy-1,4-naphthaquinone, m.p. 214–215° (Found: C, 66·2; H, 5·0. Calc. for $C_{12}H_{10}O_4$: C, 66·0; H, 4·6%), formed from 2,7-dimethoxynaphthalene by another oxidant.*

1-Bromo-2,7-dimethoxynaphthalene

2,7-Dimethoxynaphthalene (20·2 g) was monobrominated by the method previously described,[6] to give a product (19·2 g), m.p. 71–76°, which, on recrystallization from 95% ethanol, afforded white prisms (16·9 g), m.p. 75·5–76·5°. Crystallization of a portion (0·58 g) of the latter material from methanol yielded prisms (0·23 g), m.p. 77·5–78°.[6,18] (Found: C, 54·3; H, 3·8; Br, 30·4. Calc. for $C_{12}H_{11}BrO_2$: C, 54·0; H, 4·2; Br, 29·9%). A further crystallization (from 95% ethanol) did not change the m.p.

A more efficient method of preparation involved the addition of bromine as a dilute solution in chloroform. To dimethoxynaphthalene (3·08 g) in chloroform (30 ml) was added bromine (0·87 ml) in chloroform (100 ml) in 2·2 hr. The mixture was left in a closed vessel for 3 days at room temp. Removal of most of the solvent, subsequent filtration, and washing of the residue with chloroform yielded a product (3·27 g), melting at 75–77°. Recrystallization from methanol gave the bromo-compound (2·83 g), m.p. 77·5–78°.

Oxidation of 1-bromo-2,7-dimethoxynaphthalene

(1) A solution of chromium trioxide ("AnalaR"; 5·1 g) in water (4 ml) was added, from a burette in 4 min, to 1-bromo-2,7-dimethoxynaphthalene (1·65 g) in acetic acid (40 ml) and water (12 ml). Water (3 ml) was used to wash the residual chromic acid from the burette into the reaction mixture. After 15 min the product was diluted with water to 500 ml. Filtration and washing of the residue with water gave a light brown solid (0·66 g), m.p. about 213°, which, on treatment with boiling acetic acid and hot filtration, afforded a residue of light orange-brown prisms of the quinone (0·09 g; m.p. 299–302°; see Section 2 below) and a filtrate (5 ml). The latter was cooled and filtered, giving a residue (0·02 g, m.p. about 281–297°) and a filtrate, which was diluted with water to 100 ml, to produce a precipitate (0·42 g, m.p. below 169°). Chromatography on alumina failed to isolate a pure compound from this precipitate.

(2) To 1-bromo-2,7-dimethoxynaphthalene (2·83 g) in acetic acid (89 ml) was added chromium trioxide ("AnalaR"; 8·9 g) in water (18 ml) from a burette in 50 min. The maximum temp of the mixture was 46° (external cooling). The residual oxidant was washed from the burette into the mixture with water (4 ml). The product was then kept at 50° for 30 min. Dilution with water (800 ml) preceded filtration and washing of the residue (R) with water.

* Forthcoming paper.

[18] R. Adams, M. W. Miller, F. C. McGrew and A. W. Anderson, *J. Amer. Chem. Soc.* **64**, 1795 (1942).

The filtrate was extracted with chloroform. The dried (Na_2SO_4) and concentrated extract was chromatographed on alumina. After development by chloroform, the same solvent was used to elute the yellow lowest band. Seven other, small bands were discarded. The material obtained by removal of solvent from the eluate was crystallized twice from acetic acid, to yield yellow-orange prisms (S; 4 mg), m.p. 299·5–302·5°.

A solution of the residue (R; 0·50 g) in chloroform was chromatographed on alumina. Development with chloroform afforded a broad yellow band at the bottom of the column, an intermediate narrow yellow band, and a narrow brown band at the top of the column. The yellow bands were eluted by chloroform, whilst the brown portion of the column was extruded and extracted with hot acetic acid.

The eluate from the broad yellow band was collected in two portions, the first eluted having about three times the volume of the second. Removal of solvent from the larger portion, followed by recrystallization from acetic acid, gave deep yellow prisms (0·02 g), m.p. 300·5–302°, a trace of which yielded a purple solution with concentrated sulphuric acid. The mixture of this product and S (see above) was crystallized from acetic acid, to give deep yellow prisms of *5-bromo-3,6-dimethoxy-1,4-naphthaquinone*, m.p. 302·5–304° with sublimation. (Found: C, 48·3; H, 3·1; Br, 27·2. $C_{12}H_9BrO_4$ requires: C, 48·5; H, 3·1; Br, 26·9%).

Removal of the solvent from the smaller portion of the eluate from the broad yellow band afforded only a small quantity of solid, m.p. 282–283°, presumably impure 5-bromo-3,6-dimethoxy-1,4-naphthaquinone.

Evaporation of the chloroform from the eluate from the narrow yellow band gave a trace of solid m.p. 153–189°.

The extract from the brown band was shown to contain a small quantity of an aromatic carboxylic acid, melting at about 203°.

(3) In the above oxidations the molar ratio of chromium trioxide to bromodimethoxynaphthalene was 8. The use of smaller proportions of the oxidant (molar ratios of 3 and 2) was less satisfactory. Wheeler and Mattox[18] employed a molar ratio of 5 for the oxidation of a derivative of naphthalene.

(4) Unchanged 1-bromo-2,7-dimethoxynaphthalene was the only compound isolated after an attempt to oxidize it with di-t-butyl chromate.[19]

Oxidation of 1,6-*dibromo*-2,7-*dimethoxynaphthalene*

Dibromodimethoxynaphthalene (73·5 g) was oxidized as before.[1] After dilution of the reaction product with water, filtration afforded a residue (K, 30·3 g), which was treated with toluene (1·2 l.). Subsequent filtration left a residue (2·5 g), which did not melt below 360° and of which a small proportion dissolved in aqueous sodium hydrogen carbonate.

The toluene solution was chromatographed (alumina). Development with toluene was followed by elution of the pink, lowest band with the same solvent, giving a yellow eluate (L). The column then showed a yellow band (at the bottom), a deep pink band, and several small, mainly dark brown bands (at the top). The yellow (M) and deep pink bands were extruded and separately extracted with hot acetic acid. The extract from the deep pink band was concentrated to 100 ml and then diluted with water to 400 ml. From the resulting precipitate (1·0 g) and also from the yellow eluate (L) no pure compound was isolable.

The extract from the yellow band (M) was concentrated and, after the addition of charcoal, was filtered while hot. The precipitate (N) from the cold filtrate was recrystallized from acetic acid, to yield a product (1·30 g), m.p. 258·5–260°. Three more crystallizations from acetic acid gave deep yellow acicular crystals of 6-bromo-2,7-dimethoxy-1,4-naphthaquinone, m.p. 260–260·5° (cf. Ref. 1; sublimate in m.p. tube). (Found: C, 48·7; H, 2·8; Br, 26·9. Calc. for $C_{12}H_9BrO_4$: C, 48·5; H, 3·1; Br, 26·9%).*

The aqueous filtrate from the residue K (see above) was extracted with chloroform. The solvent was removed from the dry (Na_2SO_4) extract, giving a very viscous material, which was treated with a mixture of acetic acid and petroleum ether (b.p. 80–100°). The product was filtered, and the residue was washed with acetic acid and then with water. The resulting solid (1·1 g) was with acetic agitated

* See spectrogram (1) and cf. Sadtler spectrogram 15446 for the chloro-analogue.[1]

[18] A. S. Wheeler and W. J. Mattox, *J. Amer. Chem. Soc.* **55,** 686 (1933).

[19] R. V. Oppenauer and H. Oberrauch, *Anal. Asoc. quim. Argentina* **37,** 246 (1949); *Chem. Abstr.* **44,** 3871 (1950).

acid, the hot mixture being filtered to give a residue (P). The cold filtrate yielded a precipitate (0·7 g) which was treated with hot chloroform (80 ml). After cooling, the mixture was filtered (filtrate Q). Most of the residue dissolved, with effervescence, in aqueous sodium hydrogen carbonate. The addition of charcoal was followed by filtration and then by acidification of the filtrate with hydrochloric acid. The consequent white precipitate, after washing with water, weighed 0·29 g and m.p. was 229–229·5° (decomp). Two crystallizations from acetic acid afforded white prisms of *5-bromo-2-carboxy-4-methoxyphenylglyoxal* (V), m.p. 230·5–231·5° with decomp and white sublimation. (Found: C, 41·8; H, 2·5; Br, 27·7; O, 27·8; MeO, 10·6; equiv. wt. 278. $C_{10}H_7BrO_5$ requires: C, 41·8; H, 2·5; Br, 27·8; O, 27·9; MeO, 10·8%; equiv. wt. 287).* The compound gave a silver mirror with ammoniacal silver nitrate solution.

The filtrate (Q) was mixed with petroleum ether (120 ml; b.p. 80–100°), to precipitate a solid (0·21 g), which recrystallized from acetic acid as brownish-maroon needles, m.p. 236·5° (decomp). The latter material and the residue P (see above; 0·07 g) were crystallized thrice from acetic acid, yielding a product, which, after washing with aqueous sodium hydrogen carbonate and then with water, weighed 0·08 g and had m.p. 244°. Two further crystallizations from acetic acid gave deep brown-red needles of *3,8-dibromo-7-methoxy-1,2-naphthaquinone*, m.p. 244–244·5°. (Found: C, 38·0; H, 1·6; Br, 46·3; O, 14·3; MeO, 8·8. $C_{11}H_6Br_2O_5$ requires: C, 38·2; H, 1·7; Br, 46·2; O, 13·9; MeO, 9·0%).† A less pure specimen of this compound was formerly[1] designated as "4,7-dibromo-3,6-dimethoxy-1,2-naphthaquinone".

The mother-liquor from the precipitate (N) yielded, on dilution with an equal volume of water, a deposit which was recrystallized from acetic acid. The product, when it had been washed with aqueous sodium hydrogen carbonate and with water, was crystallized from a mixture (1 : 1 by volume) of petroleum ether (b.p. 80–100°) and toluene (charcoal) and then from acetic acid (charcoal), affording a substance (0·12 g), m.p. 125–128°. A final crystallization from methanol (charcoal) gave needles of 1,6-dibromo-2,7-dimethoxynaphthalene, m.p. 127·5–128·5° and mixed m.p. with an authentic sample 129–130°.

Coupling of p-nitrobenzenediazonium chloride with bromo- and dibromo-naphthalene-2,7-diol

Many experiments were done on the coupling of *p*-nitrobenzenediazonium chloride,[2] reduction of the resultant dyes and acetylation of the products of reduction. In only one case (see next paragraph) was an apparently pure compound isolated. Chromatography indicated complex mixtures. The dibromodiol used in the unsuccessful experiments melted at 151·5–154·5° (cf. Ref. 3).

To *p*-nitroaniline (0·23 g; 0·0017 mole) in 10 N HCl (0·50 ml) and water (0·60 ml) were added ice (2·5 g) and then sodium nitrite (0·132 g) in water (0·88 ml).[21] The solution of diazonium salt was poured into a solution of 1,6-dibromonaphthalene-2,7-diol (0·26 g; 0·00082 mole; m.p. 162·5–163°), sodium thiosulphate[15] (pentahydrate; 0·22 g), and sodium hydroxide (0·35 g) in water (4 ml). The product was acidified with N HCl (10 ml). The amorphous reddish-brown washed (water) dye (0·4 g), m.p. 195° (decomp), was recrystallized from a filtered solution in cold pyridine, to give the deep reddish-brown amorphous *6-bromo-1-p-nitrobenzeneazonaphthalene-2,7-diol* (0·07 g), m.p. 270° (decomp). (Found: C, 50·1; H, 2·9; Br, 21·0; N, 11·3. $C_{16}H_{10}BrN_3O_4$ requires: C, 49·5; H, 2·6; Br, 20·6; N, 10·8%). The compound formed, in concentrated sulphuric acid, a deep purple solution, which, on dilution with water, gave a red-brown solution.

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* See spectrogram (3).

† See spectrogram (2).

[21] K. H. Saunders, *The Aromatic Diazo-compounds and Their Technical Applications* (2nd Ed.) p. 6. Arnold, London (1949).

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CYCLOPROPANES FROM 1°-ALKYL CHLORIDES BY α-ELIMINATION

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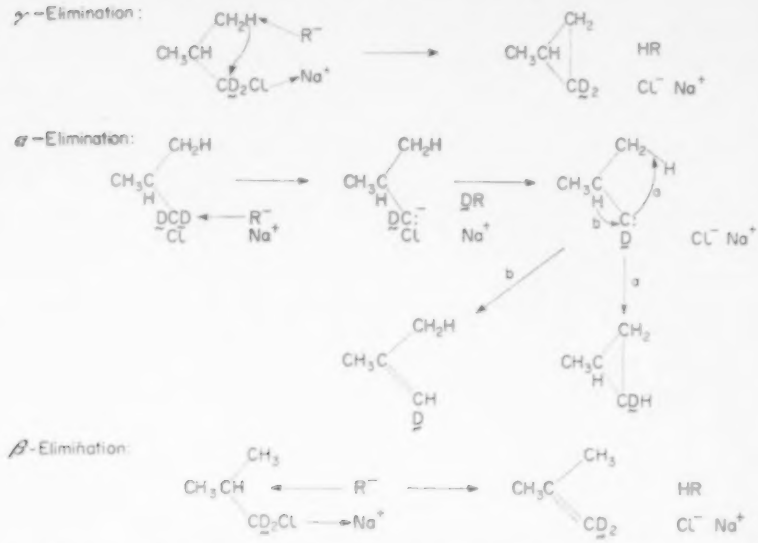
Abstract—The reaction of appropriate primary alkyl chlorides with sodium or potassium gives cyclopropanes, in addition to previously observed hydrocarbons. Through the use of tritium and deuterium, it was proved that isobutyl chloride produces methylcyclopropane by a mechanism involving α-elimination to a carbene and insertion into a carbon–hydrogen bond. Isobutylene is formed by α- and β-elimination. No α-elimination (as reflected by cyclopropane production) is found with s-butyl chloride, methyl isobutyl ether or with methyl isobutyl sulfide.

1,1-DIMETHYLCYCLOPROPANE is the major product of the treatment of neopentyl chloride with sodium[1,2] or sodium alkyls.[3] This unique reaction is the more striking in that no cyclopropane derivatives are reported in the Wurtz reaction[4] or in the reaction of 1-chlorohexane with sodium ethyl.[3] Now, thanks to the higher analytical power of gas liquid partition chromatography (g.l.p.c.), cyclopropane derivatives are found to be minor products in the reaction of other primary chlorides with sodium or potassium.

Thus, the reaction of sodium in cyclohexane with n-propyl chloride gives cyclopropane (4 per cent of the C_nH_{2n} fraction) and propylene (96 per cent), in addition to propane and hexane. n-Butyl chloride, under the same conditions, gives methylcyclopropane (7 per cent), 1-butene (86 per cent), *trans*-2-butene (4 per cent) and *cis*-2-butene (3 per cent). The latter products are probably formed by the isomerization of 1-butene.[5] Isobutyl chloride yields methylcyclopropane in significantly larger amount (35 per cent of the C_4H_8 fraction). These values are to be compared with those for neopentyl chloride which gives dimethylcyclopropane exclusively as the C_5H_{10} product.[2] It is significant that isobutyl *bromide* gives only a trace of methylcyclopropane (3 per cent of the C_4H_8 fraction), while methyl isobutyl ether and methyl isobutyl sulfide react with sodium and n-propyl chloride to give isobutylene and no methylcyclopropane. While both sodium and potassium produce methylcyclopropane from isobutyl chloride, lithium gives none, a point to which we shall return later. The secondary chloride, 2-chlorobutane, gives no methylcyclopropane under any conditions, as shown in Table 1. In summary, primary chlorides with γ-hydrogen can now be expected to give varying amounts of cyclopropanes when treated with sodium or potassium or their corresponding alkyl derivatives.

The mechanism of the production of the cyclopropanes has been formulated as a γ-elimination by Whitmore. His first proposal, involving homolytic elimination by way of an α,γ-diradical, was followed by an ionic elimination involving removal of a γ-proton by sodium alkyl and an intramolecular ring closure of the displacement

[1] F. C. Whitmore, A. H. Popkin and J. R. Pfister, *J. Amer. Chem. Soc.* **61**, 1616 (1939).
[2] F. C. Whitmore, A. H. Popkin, H. I. Bernstein and J. P. Wilkins, *J. Amer. Chem. Soc.* **63**, 124 (1941).
[3] F. C. Whitmore and H. D. Zook, *J. Amer. Chem. Soc.* **64**, 1783 (1942).
[4] Cf. W. Hückel, A. Krämer and F. Thiele, *J. Prakt. Chem.* **142**, 207 (1935).
[5] W. O. Haag and H. Pines, *J. Amer. Chem. Soc.* **82**, 387 (1960).



type. Since removal of protons by sodium alkyl from hydrocarbons is an unknown reaction,[6] one would consider a concerted version of proton removal and displacement as energetically more attractive.

TABLE 1. C_4H_8 PRODUCTS FROM 2-CHLOROBUTANE AND ALKALI METALS

	Li	Na	K
1-Butene	66	68	60
trnas-Butene	24	17	28
cis-Butene	10	15	12
Methylcyclopropane	—	—	—

Another mechanism involves α-elimination by abstraction of an α-proton, loss of chloride ion and intramolecular insertion of the resulting carbene into the γ-carbon–hydrogen bond. The credibility of the first step is not demonstrated by directly analogous reactions, but rather by extrapolations from related reactions. Removal of α-proton is very easy with chloroform where three chlorine atoms stabilize the resulting carbanion;[7] in methylene chloride with only two chlorine atoms to stabilize the resulting carbanion, the proton can still be removed, albeit only by the action of the stronger bases of the alkyl lithium type;[8] in alkyl chlorides, even stronger bases would be required, since the resulting carbanion would now be stabilized by only a single chlorine atom. Indeed, Hill *et al.* find some α-elimination in the conversion of n-octyl bromide to octene-1 with sodium amide in liquid ammonia and employ α-elimination with terminal step b (Chart 1) as explanation.[9] The second step, the loss of chloride

[6] See, however, A. I. Shatenshtein, L. N. Vasil'eva, N. M. Dykhno and E. A. Izraelevich, *Dokl. Akad. Nauk SSSR.* **85,** 381 (1952).
[7] J. Horiuti and Y. Sakamoto, *Bull. Chem. Soc. Japan* **11,** 627 (1936).
[8] G. L. Closs and L. E. Closs, *J. Amer. Chem. Soc.* **81,** 4996 (1959).
[9] D. G. Hill, W. A. Judge, P. S. Skell, S. W. Kantor and C. R. Hauser, *J. Amer. Chem. Soc.* **74,** 5599 (1952); S. M. Luck, D. G. Hill, A. T. Stewart, Jr. and C. R. Hauser, *J. Amer. Chem. Soc.* **81,** 2784 (1959). See also U. Schöllkopf and M. Eistert, *Agnew. Chem.* **72,** 349 (1960).

ion, is exemplified by the intermediacy of dichlorocarbene[10] and chlorocarbene.[8] The third step, the insertion of the alkylcarbene into the γ-carbon-hydrogen bond, is the typical reaction of carbenes, more commonly observed, however, as the intermolecular[11] rather than the intramolecular reaction.[12–15]

To define the mechanism, the fate of deuterium in the reaction of 1-chloro-1,1-dideutero-2-methylpropane (the labeled isobutyl chloride of Chart 1) with sodium was determined. This mode of attack on the mechanistic problem follows that used by Hill *et al.* in their investigation of α-elimination.[9] The labeled isobutyl chloride was prepared by a two-step sequence involving reduction of ethyl isobutyrate with lithium aluminum deuteride and treatment of the resulting 1,1-dideutero-2-methylpropanol-1 with thionyl chloride. It was isolated in pure form by preparative g.l.p.c. and was found by mass spectrographic analysis to consist of >90 per cent dideuterated material. When this chloride was treated with sodium metal, monodeuterated methylcyclopropane was produced, containing less than 1 per cent of dideuterated material. Since γ-elimination would lead exclusively to dideuterated material and α-elimination followed by insertion (terminal step *a* of Chart 1) would lead exclusively to monodeuterated methylcyclopropane, only the α-elimination-insertion path is compatible with the experimental results. Quantitatively, it can be asserted confidently that less than 2 per cent of the methylcyclopropane is formed by γ-elimination.

The distribution of deuterium in the isobutylene produced along with the methylcyclopropane fixes the ratio of α- to β-elimination. Isobutylene formed by α-elimination-rearrangement (terminal step *b* of Chart 1) will retain only one deuterium atom, whereas isobutylene formed by conventional β-elimination will retain both deuterium atoms. In this experiment, α-elimination-rearrangement predominated (67 per cent) over β-elimination (33 per cent). Distribution of rearrangement and insertion within the α-elimination path cannot be determined with much assurance, because of the high probability that isobutylene reacts further with isobutyl sodium. In this connection, it has been found that the addition of cyclohexane strongly inhibits the production of isobutylene and methylcyclopropane without eliminating isobutane.

The argument for the intervention of a carbene is strengthened by noting (Table 2) how closely the product distribution in the reaction of primary chlorides with sodium parallels that observed by Friedman and Schechter in the decomposition of *p*-toluenesulfonylhydrazones of the related aldehydes.[12]

An estimation of the magnitude of the isotope effect has been obtained from experiments using tritium-labeled isobutyl chloride. The results are shown in Table 3. From the identity of the activities of the isobutane and isobutene in the lithium reaction, it is clear that no α-elimination is involved. The increased radioactivity in isobutane (and the decreased activity in isobutene) is a reflection of the extent to which α-elimination is a component of the reaction. By this criterion potassium leads to more α-elimination than sodium. On the assumptions that the ratio of the activity of methylcyclopropane to that of isobutane from the lithium reaction (taken as a measure of the activity of the isobutyl chloride) is proportional to the rate of α-elimination of

[10] J. Hine, *J. Amer. Chem. Soc.* **72**, 2438 (1950).
[11] W. von E. Doering and H. Prinzbach, *Tetrahedron* **6**, 24 (1959).
[12] L. Friedman and H. Schechter, *J. Amer. Chem. Soc.* **81**, 5512 (1959).
[13] H. Meerwein and K. van Emster, *Ber. Dtsch. Chem. Ges.* **53**, 1815 (1920).
[14] L. Friedman and H. Schechter, *J. Amer. Chem. Soc.* **82**, 1002 (1960).
[15] J. W. Powell and M. C. Whiting, *Tetrahedron* **7**, 305 (1959).

hydrogen, and that the possibility of a difference in the ratio of β- to α-elimination in isobutyl chloride and tritium-labeled isobutyl chloride may be ignored, a simple calculation leads to $k_H/k_D = 1{\cdot}6$. A more refined calculation involving a correction for the second assumption leads to a value of 1·9. This isotope effect is surprisingly small and may be compared with a value of 15·5 for β-elimination in isopropyl bromide (calculated from the observed k_H/k_D ratio of 6·7[16] by the method of Swain *et al.*[17]).

TABLE 2. COMPARISON OF THE SODIUM-ALKYL CHLORIDE REACTION WITH THE ALKALINE DECOMPOSITION OF ALDEHYDE TOSYLHYDRAZONES[12]

Hypothetical carbenes	Products in %	RCl·Na	R = NNHTs
$CH_3CH_2\ddot{C}H$	cyclopropane	4	2
	propene	96	98
$CH_3CH_2CH_2\ddot{C}H$	methylcyclopropane	7	5
	butene-1	86	92
	cis-butene	3	1
	trans-butene	4	2
$(CH_3)_2CH\ddot{C}H$	methylcyclopropane	35	45
	isobutene	65	55
$(CH_3)_2C\ddot{C}H$	1,1-dimethyl-cyclopropane	>95[a]	>92

TABLE 3. RELATIVE RADIOACTIVITIES[a] IN PRODUCTS FROM THE REACTION OF 1-CHLORO-2-METHYLPROPANE-1-^{3}H[b]

	Li	Na	K
isobutane	1·00	1·10	1·29
isobutene	1·04	0·79	0·70
methylcyclopropane	—	0·64	0·63

[a] The average of the activities of isobutane from the lithium reaction are taken as 1·00. [b] All reactions were run on the same sample of labeled isobutyl chloride.

The failure of lithium to give methylcyclopropane can be ascribed either to the inability of lithium alkyl to remove α-hydrogen or to the inability of the resultant lithium chloroalkyl to lose chloride ion and to form the carbene. The reaction of lithium isopropyl with methylene chloride according to Closs[8] leads to isobutylene (79 per cent) and methylcyclopropane (21 per cent). It is apparent that lithium alkyl has added to chlorocarbene forming lithium 1-chloroisobutyl which has then lost chloride ion to form the carbene and thence methylcyclopropane. The failure of lithium in the reaction of isobutyl chloride is thus due to the inability of lithium isobutyl to remove α-hydrogen.*

EXPERIMENTAL

Reactions of alkyl chlorides with alkali metals. Reactions were carried out in a 50 ml, three-necked flask equipped with a gas inlet tube, reflux condenser and dropping funnel. The top of the reflux condenser was connected to a dry-ice trap. The alkali metals were cut into small pieces under mineral

* *Note added in proof:* G. L. Closs, Abstracts of papers presented at the 138th Meeting of the American Chemical Society, September, 1960, p. 9P and *Chem. Enging. News* **38**, No. 38, 54 (1960), as also obtained cyclopropane derivatives in the reaction of alkly lithium with methylene chloride.

[16] V. J. Shiner, Jr., *J. Amer. Chem. Soc.* **74**, 5285 (1952).

[17] C. G. Swain, E. C. Shivers, J. F. Reuwer, Jr. and L. J. Schaad, *J. Amer. Chem. Soc.* **80**, 5885 (1958).

TABLE 4. MASS SPECTRA OF ISOBUTYL CHLORIDE

m/e	unlabeled	labeled
41	44·8	25·0
42	52·6	50·0
43	100	100
44	3·3	4·5
45	0·1	0·4
75	0·50	—
76	0·41	0·21
77	3·02	0·33
78	0·30	0·25
79	1·04	2·67
80	—	0·17
81	—	0·88

TABLE 5. MASS SPECTRA OF PRODUCTS FROM 1-CHLORO-2-METHYLPROPANE-1,1-^2H

	Methylcyclopropane		Isobutylene	
m/e	Unlabeled	Labeled[a]	Unlabeled	Labeled[a]
27	6·7	7·3		
28	20·9	19·9		
29	30·3	31·9		
30	14·2	26·3		
31		11·7		
38	3·9	3·1	6·32	5·4
39	39·0	23·0	44·9	33·5
40	6·7	22·8	10·2	33·5
41	90·0	43·1	**100·0**	64·6
42	3·9	82·3	3·65	**100·0**
43	2·8	3·3		28·1
44		0·7		1·3
50	5·5	3·5		
51	4·7	4·0		
52	1·2	2·6		
53	8·3	3·0		
54	3·5	6·3		
55	25·6	4·9	16·0	5·4
56	**100·0**	24·6	44·5	22·5
57	4·3	**100·0**	1·98	63·3
58		4·4		28·3
				1·8

[a] From the reaction described here.

oil, washed with solvent and transferred to the flask. After sweeping with nitrogen and heating to reflux, the alkyl halide with more solvent was added from the dropping funnel. A slow stream of nitrogen was passed through the mixture during the reaction. In most runs, 20 mmoles of alkali metal and alkyl halide in 10 ml cyclohexane were used. When the liquid in the dry-ice trap did not increase any more (ca. 3 hr with lithium and sodium; 0·5–1 hr with potassium) the trap was disconnected and any excess of alkali metal decomposed with methanol. Water was added and the organic layer washed several times with water. The Wurtz hydrocarbons $(C_nH_{2n-1})_2$, the only products remaining in the solvent were separated by g.l.p.c. on a 2 m OX column (Perkin–Elmer) or a 4 m silicone column.

The contents of the dry-ice trap were analyzed by g.l.p.c. at room temperature on a 1/4″, 6 m column consisting of a polyether $[CH_3(OCH_2CH_2)_4OCH_3]$ on firebrick. Samples of the liquid condensate were drawn directly into a syringe, in order to avoid fractionation. Cyclopropanes and other unknown substances were identified by their mass spectra. It has been shown that, for a wide range of hydrocarbons, peak areas represent the composition within the error of determination.[18] In a typical run, from 1·84 g isobutyl chloride (20 mmoles) and 0·46 g sodium (20 mmoles), 0·78 g (56%) volatile products were obtained, consisting of isobutane (57%), isobutene (29%) and methylcyclopropane (14%). Other results may be found in Tables 1 and 2.

1-*Chloro*-2-*methylpropane*-1,1-^{2}H. Methyl isobutyrate (6·1 g, 60 mmoles) was reduced with 1·1 g (25 mmoles) of lithium aluminum deuteride (95·6%, Metal Hydrides, Inc.) in refluxing ether (50 ml). A small excess of ester was used in order to assure complete utilization of the hydride. The crude isobutyl alcohol obtained by distillation was converted to the chloride with thionyl chloride in pyridine. Pure isobutyl chloride was isolated by g.l.p.c. at 35° in a Perkin–Elmer, 1″ preparative column packed with didecylphthalate on firebrick. From the mass spectrum in Table 4, the sample contained 90% of the d_2 compound. The peaks corresponding to the C_3 ions show the absence of deuterium quite clearly. The group of peaks of mass 75–81 corresponds to the parent minus methyl. The parent peaks themselves are too weak to be of use.

This material (1 mmole) was treated with 1 mmole sodium in 0·5 ml cyclohexane in a sealed, evacuated tube (1 hr at 80°). The volatile contents of the tube were transferred to a bypass system on a vacuum line and subjected to g.l.p.c. on the 6 m polyether column. The mass spectra of the isolated methylcyclopropane and isobutene are shown in Table 5.

1-*Chloro*-2-*methylpropane*-1-^{3}H. An ethereal solution (150 ml) of diazoisobutane was prepared from 15 g N-nitroso-isobutylurea according to the directions of Bruchhausen[19].

Tritiated hydrogen chloride, generated by dropping tritiated water (10 mC/g) on phosphorus pentachloride was swept into the cooled diazoisobutane solution by a slow stream of nitrogen. Decoloration was effected by using 0·5 ml water. The ethereal solution was dried, neutralized by shaking with 2 g anhydrous potassium carbonate for 0·5 hr, diluted with 10 ml toluene and distilled through a 20 cm helix-packed column giving fractions of b.p. 55–64° (0·7 g), 64–69° (3·6 g, 40%) and 69–90° (1·3 g). The main fraction was almost pure isobutyl chloride. Analysis by g.l.p.c. showed the main impurities to be ether and traces of olefins, which were removed by shaking with an equal volume of conc. sulfuric acid. The final product contained less than 2% of isomeric butyl chlorides.

The labelled isobutyl chloride (5 mmoles) reacted with 5 mmoles of sodium in 5 ml of refluxing cyclohexane. The volatile products were analyzed on the 6 m polyether column which was part of a g.l.p.c.–flow counter system.[20] All runs were made at the same flow rate, and relative activities were measured in counts/mm^2 peak area on the mass track. The results are shown in Table 3.

Acknowledgements—We wish to acknowledge our gratitude to the Esso Research and Engineering Company for its generous support of this work; and to express our thanks to Mr. P. P. Gaspar for his assistance in some of the preparative work and in the mass spectrometric analyses.

[18] E. M. Fredericks and F. R. Brooks, *Analyt. Chem.* **28**, 297 (1956).
[19] F. v. Bruchhausen and H. Hoffmann *Ber. Dtsch. Chem. Ges.* **75**, 1593 (1941).
[20] R. Wolfgang and R. S. Rowland, *Analyt. Chem.* **30**, 903 (1958); W. von E. Doering and H. Prinzbach, *Tetrahedron* **6**, 24 (1959).

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THE ABSOLUTE CONFIGURATION OF *TRANS*-1,2-DIMETHYLCYCLOPROPANE

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Abstract—By application of the newly discovered fact that 1° alkyl chlorides with γ-hydrogen form cyclopropanes on treatment with sodium metal, (−)-*trans*-1,2-dimethylcyclopropane has been prepared from (+)-1-chloro-2-methylbutane. Rigorous assignment of configuration to the isomeric *cis*- and *trans*-dimethylcyclopropanes is thereby achieved. The absolute configuration, (1R : 2R) *trans*-1,2-dimethylcyclopropane, can be assigned to the (−) enantiomer by several lines of argument and agrees with that calculated by Fitts.

1,2-DIMETHYLCYCLOPROPANES have been used so often as reference substances in studies of the mechanism of the addition of carbenes to olefins[1–3] that a firm establishment of *cis* and *trans* configuration is clearly desirable. With previous assignment having been based on the empirical Auwers–Skita rule,[1,4] a more rigorous and positive assignment can be based on the theoretical necessity that the *trans* isomer alone may exist in optically active form. In this paper, we report the preparation in optically active form of that isomer previously, and now correctly, considered to be *trans*.

The preparation is accomplished by an application of the cyclopropane synthesis reported in the preceding paper.[5] The dextrorotatory chloride obtained from laevorotatory 2-methyl-1-butanol[6] was treated with sodium to give a mixture of C_5 hydrocarbons in 63 per cent of theory. Analysis of this mixture by gas liquid partition chromatography (g.l.p.c.) showed it to consist of isopentane (55·6 per cent), 2-methylbutene-1 (23·4 per cent), ethylcyclopropane (9·3 per cent) and *trans*-1,2-dimethylcyclopropane (11·7 per cent). The two cyclopropane derivatives were identified by retention times and comparison of mass spectra with those of authentic samples. *cis*-1,2-Dimethylcyclopropane may be formed in very small amount, but in the absence of adequate identification cannot be considered to be an established product. The high degree of stereoselectivity is presumably a reflection in the transition state of the thermodynamically greater stability of the *trans* isomer.

The ratio of 1,2-dimethylcyclopropane to ethylcyclopropane is a measure of the ability of the intermediate carbene to discriminate between 2° and 1° hydrogen. Methylene generated photochemically from diazomethane shows no discrimination[7] in *solution*, but does discriminate in the *gas phase* at the higher total pressures.[8] This difference has been ascribed to the intervention of "hot" methylene molecules. In solution, formed with excess energy, these react on every collision with little or no discrimination; in the gas phase, they are cooled to thermal methylene molecules by

[1] W. von E. Doering and P. M. LaFlamme, *J. Amer. Chem. Soc.* **78,** 5447 (1956).
[2] P. S. Skell and R. C. Woodworth, *J. Amer. Chem. Soc.* **78,** 4496 (1956).
[3] H. M. Frey, *J. Amer. Chem. Soc.* **80,** 5005 (1958); *Proc. Roy. Soc.* **251,** 575 (1959).
[4] J. Baudrenghien, *Bull. Soc. Chim. Belg.* **38,** 172 (1929).
[5] W. Kirmse and W. von E. Doering, *Tetrahedron* **11,** 266 (1960).
[6] H. C. Brown and C. Groot, *J. Amer. Chem. Soc.* **64,** 2563 (1942).
[7] W. von E. Doering, R. G. Buttery, R. G. Laughlin and N. Chaudhuri, *J. Amer. Chem. Soc.* **78,** 3224 (1956); D. B. Richardson, M. C. Simmons and I. Dvoretzky, *J. Amer. Chem. Soc.* **82,** 5001 (1960).
[8] H. M. Frey and G. B. Kistiakowsky, *J. Amer. Chem. Soc.* **79,** 6373 (1957).

prior collision with inert gas and then react with discrimination favoring 2° hydrogen over 1° by a factor of about 1·7. In the reaction of alkyl halide with sodium, the intermediate carbene is generated in a way[8] which is not expected to produce methylene with excess energy. In the present example reaction with 2° hydrogen is favored by a factor of 1·9 over reaction with 1° hydrogen. This observation can be considered to support the hypothesis that "hot" methylene is the reactive species in the photolysis of solutions of diazomethane.

MASS SPECTRA

ethylcyclopropane			*trans*-1,2-dimethylcyclopropane	
m/e	obs.	lit[a]	obs.	auth.[b]
71	2·0	1·5	3·0	3·5
70	32	28	78	62
69	1·0	1·0	2·2	2·5
56	2·5	2·3	4·2	4·6
55	74	50·2	100	100
54	1·0	2·0	2·2	2·5
53	4·3	6·3	8·3	8·4
43	4·5	3·8	3·0	3·8
42	100	100	48	44
41	36	42	36	37
40	6·5	9·1	4·7	4·8
39	22	38	27	26
38	2·3	6·2	2·2	2·3

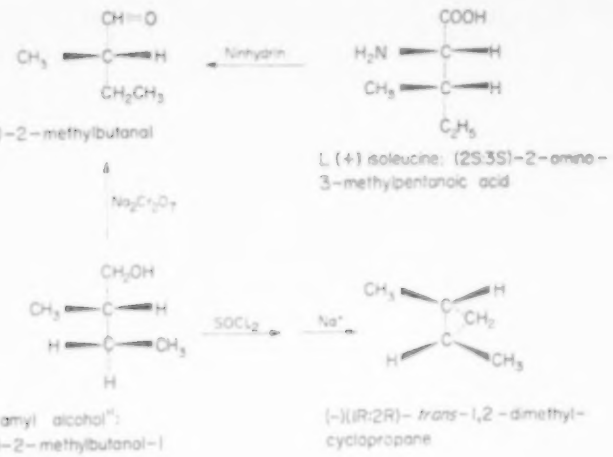
[a] American Petroleum Institute Research Project 44, Mass Spectrum 1652.
[b] From a sample prepared by D. L. MacDuffie.

The specific rotation of *trans*-1,2-dimethylcyclopropane was estimated by enriching a crude fraction of b.p. 28·0–28·5° to 26 per cent by separation on a preparative g.l.p.c. column. This material was then purified by passing many small batches through a small column of sufficient resolution to allow isolation of pure material, the specific rotation of which was −46·0°. Barring the unlikely possibility of partial racemization during the reaction of the active amyl chloride with sodium, this value may be taken as that of fully resolved material. Although the starting 2-methylbutanol-1 had a rotation (−5·71°) somewhat below the most reliable value (−5·88°),[9] the discrepancy is due almost certainly to contamination by isomeric rather than enantiomeric alcohol.

The proof of structure of *trans*-1,2-dimethylcyclopropane is therefore complete, and, with it, the conclusion that methylene and dibromocarbene add to *cis*- and *trans*-butene by *cis*-addition[1] is given an unquestionably sound basis.

The absolute configuration of (−) *trans*-1,2-dimethylcyclopropane may now be deduced. Its configuration relative to (−) 2-methylbutanol-1 is clear enough. Neither by analogy with known reactions nor by application of current mechanistic theory is there reason to suspect that the conversion to chloride and its subsequent closure to cyclopropane would jeopard the assymetric center in any way.

[9] F. v Falkenhausen and C. Neuberg, *Biochem. Z.* **242**, 482 (1931).



There are at least three arguments in the literature that relate 2-methylbutanol-1 to tartaric acid, the absolute configuration of which has been determined by X-ray crystallography.[10] One is by Freudenberg and Hohmann[11], another is by Crombie and Harper[12] and a third is by Mills and Klyne[13]. All agree in assigning the (S) configuration to (−)-2-methylbutanol-1.[14]

There is another more direct sequence relating d(−)amyl alcohol to L(+)isoleucine in which both are connected to (+)-2-methylbutanal, the former by oxidation with sodium dichromate,[15] the latter by reaction with ninhydrin.[16] Since the absolute configuration of the enantiomorphic isoleucines has been determined by Trommel and Bijvoet by X-ray crystallography[17] in the sense that D(−)isoleucine is (−)(2R:3R)-2-amino-3-methylpentanoic acid, d(−)amyl alcohol has the configuration (S)-2-methylbutanol-1. With complete consistency prevailing between the chemical interrelationships and the absolute configurational determinations by X-ray, the absolute configuration of (−)(S)-2-methylbutanol-1 is established. The absolute configuration of laevorotatory *trans*-1,2-dimethylcyclopropane is therefore (1R:2R).

Establishment of the absolute configuration of (−)(1R:2R)-*trans*-1,2-dimethylcyclopropane permits another comparison with the theory of optical activity.[18] The theoretical calculation of the specific rotation of the (1R:2R) enantiomer has been made quite recently by Fitts[19] on the basis of Kirkwood's theory. The calculated value (−16·0°) agrees in sign with that of the observed value (−46·0°). Better quantitative agreement might have been expected since a single conformation probably suffices to describe the molecule. The entire illustration consisting of the theoretical calculation,

[10] J. M. Bijvoet, A. F. Peerdeman and A. J. van Bommel, *Nature, Lond.* **168**, 271 (1951); A. J. van Bommel and J. M. Bijvoet, *Acta Cryst.* **11**, 61 (1958).
[11] K. Freudenberg and W. Hohmann, *Liebigs Ann.* **584**, 55 (1953).
[12] L. Crombie and S. H. Harper, *J. Chem. Soc.* 2685 (1950).
[13] J. A. Mills and W. Klyne, *Progress in Stereochemistry* Vol. I, p. 197. Academic Press, New York (1954).
[14] R. S. Cahn, C. K. Ingold and V. Prelog, *Experientia* **12**, 81 (1956).
[15] E. J. Badin and E. Pacsu, *J. Amer. Chem. Soc.* **67**, 1352 (1945).
[16] W. S. Fones, *J. Amer. Chem. Soc.* **76**, 1377 (1954); F. Ehrlich, *Ber. Dtsch. Chem. Ges.* **40**, 2538 (1907).
[17] J. Trommel and J. M. Bijvoet, *Acta Cryst.* **7**, 703 (1954).
[18] For a review, see W. Kuhn, *Z. Electrochem.* **56**, 506 (1952).
[19] D. D. Fitts in A. Weissberger, *Technique of Organic Chemistry, Physical Methods of Organic Chemistry* (3rd Ed.) Vol. 1, Part III, Interscience, New York (1960).

the absolute X-ray configuration and the present chemical interrelationship is a strikingly simple addition to the subject of absolute configuration.

EXPERIMENTAL

(−)(1R:2R)-trans-1,2-*Dimethylcyclopropane*. The starting material, (−)(S)-2-methylbutanol-1, was obtained by the fractional distillation of enriched d(−)amyl alcohol and had $[\alpha]_D^{20}$ −5·71° (neat). The most reliable value for pure alcohol is −5·88°.[9]

This alcohol was converted by thionyl chloride in pyridine according to Brown and Groot[6] to (+)(S)-1-chloro-2-methylbutane, $[\alpha]_D^{20}$ +1·66° (neat).

The cyclization was carried out without solvent by adding 21·2 g (0·2 mole) (+)amyl chloride gradually to 4·6 g (0·2 mole) sodium in a flask equipped with a short Vigreux column, a condenser and a dry-ice trap. A slow stream of nitrogen was passed through the mixture. After all the chloride had been added, the temperature was raised to 150° for 1 hr. A total of 6·1 g (44%) material boiling below 40° was collected.

For analysis, g.l.p.c. on a 6 m column of polyether was used. The products with their relative areas follow: isopentane (140); 2-methylbutene-1 (60); *trans*-1,2-dimethylcyclopropane (23·5); ethylcyclopropane (16·5); 3-methylbutene-1 (3); and a small, unidentified peak (1·5) having the retention time of 2-methylbutene-2 and *cis*-1,2-dimethylcyclopropane. Ethylcyclopropane and *trans*-1,2-dimethylcyclopropane were isolated and identified by their mass spectra. These were measured on a Consolidated Engineering Corp., Mass Spectrometer Model 21–401 at 70 volts.

When the cyclization was carried out in 50 ml cyclohexane, 42·4 g (0·4 mole) (+)-amyl chloride was added to 9·2 g (0·4 mole) sodium fast enough to maintain gentle reflux and the flask was modified by replacing the short column by a 50 cm one fitted with a distillation head. About 19 g material boiling below 40° was collected. Since it contained 7–8% cyclohexane, the yield of C_5 hydrocarbons was 17·5 g (63%). To determine the composition of this product four analyses on the 6 m polyether column were averaged; isopentane (12·5); 2-methylbutene-1 (52·6); *trans*-1,2-dimethylcyclopropane (26·2); and ethylcyclopropane (21·2).

The crude mixture was carefully fractionated in a 50 cm helix-packed column. A fraction, b.p. 28·0–28·5°, was analyzed four times by g.l.p.c. and found to contain 13·24 ± 0·31% *trans*-1,2-dimethylcyclopropane. A solution of 2·935 g of this mixture (corresponding to 0·386 g *trans*-1,2-dimethylcyclopropane) made up to 10·00 ml with diethylene glycol dimethylether (diglyme) had an observed rotation of −1·67° (1dm tube). This corresponds to $[\alpha]_D^{20}$ −43 ± 2°.

The fraction, b.p. 28·0–28·5°, was then concentrated to 26% by passing through a 2″, 4 ft preparative silicone column (which failed to resolve the cyclopropane from its adjoining neighbors, isopentane and 2-methylbutene-1) and finally isolated pure by passing many 100 mg samples through the 1/4″, 6 m polyether column (2-methylbutene-3-and 2-methylbutene-1 were fully resolved nearest neighbors). A solution of 54·3 mg pure *trans*-1,2-dimethylcyclopropane made up to 2·00 ml with 1·885 g diglyme had α^{20} − 1·25° (1 dm tube) corresponding to $[\alpha]_D^{20}$ −46·0°.

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THE PHOTOCHEMICAL INTERCONVERSIONS OF PROVITAMIN D, LUMISTEROL, PREVITAMIN D AND TACHYSTEROL

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Abstract—This paper summarizes the results of recent investigations into the photochemical isomerizations in the vitamin D field which were the subject of further research in our laboratories during the last decade. A new scheme is proposed showing the various reactions occurring during irradiation of a provitamin D. The quantum yields of these reactions at 2537 Å were determined. On the basis of these data the effect of the wavelength of the light used on the yields of products is explained. Emission spectra of ergosterol and its photoisomers were measured at 80°K. No phosphorescence was observed. Some aspects of the mechanism of the photochemical cyclizations, ring openings and the *cis/trans* isomerization are discussed.

(a) *The stoicheiometric reaction pattern*

ABOUT five years ago the results of tracer experiments with ^{14}C-labelled provitamin D as well as a theoretical consideration of the quantum yields of the (pre)vitamin D

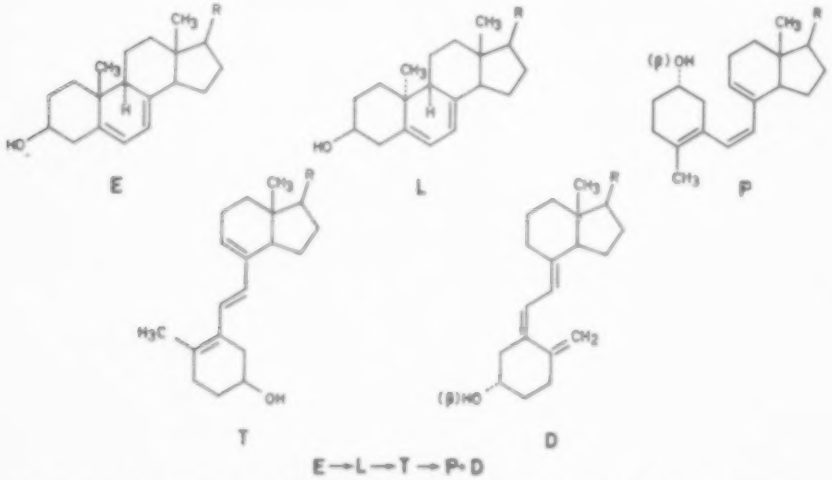

FIG. 1. The Windaus' scheme for the photoisomerization of provitamin D. With R = C_9H_{17}: E = ergosterol; L = lumisterol$_2$; P = pre-ergocalciferol; T = tachysterol$_2$; D = ergocalciferol.

formation led to the conclusion that the scheme of the photochemical formation of vitamin D from provitamin D via lumisterol and tachysterol, as given by Windaus

[1] E. Havinga, A. L. Koevoet and A. Verloop, *Rec. Trav. Chim.* **74**, 1230 (1955); and other papers in this series; For a review see H. H. Inhoffen and K. Irmscher, *Fortschritte der Chem. org. Naturstoffe* **17**, 70 (1959).

(Fig. 1) and commonly accepted for twenty years, could no longer be upheld.[1] Even upon incorporation of the discoveries of Velluz concerning the occurrence of previtamin D and the reversibility of at least some of the reactions,[2] the old picture could not give an adequate description of the experimental results. New schemes were suggested but short-cut attempts to prove the correctness of one of these gave no definite results.

It was necessary that a complete analysis of the reaction mixtures obtained with different irradiation times from each of the isomers concerned should be undertaken. In this manner the necessary data for unravelling the pattern of simultaneous and consecutive reactions that occur during prolonged irradiation of, for example, provitamin D solutions could be obtained. This work was started in 1956.

Solutions of each of the four isomers ergosterol (E), lumisterol$_2$ (L), tachysterol$_2$ (T) and pre-ergocalciferol (P) were irradiated with light of suitable wavelength. In each case the composition of the reaction mixture as a function of degree of photochemical conversion was determined. The rate of reaction was chosen sufficiently low to avoid the complicating "film effect" resulting from inhomogeneity of the irradiated solution.

E was determined by precipitation with digitonin. The concentration of P was found from the increase in ultra-violet absorption after thermal equilibrium P $\rightleftharpoons$ D had been set up. For T, a direct spectrophotometric determination at 313–320 mμ proved to be adequate. L was not determined directly, except in favourable cases where its concentration was large enough to allow of spectrophotometric determination. In one instance the presence of L was established and its amount evaluated by the isolation of lumisterol$_2$-3,5-dinitrobenzoate. Quantum yields were determined using uranyl oxalate actinometry.

Extrapolation of the percentage composition of the reaction mixture to zero time indicated both qualitatively and quantitatively the primary products formed from each of the compounds by photochemical conversion. For example, we represent the data obtained by irradiation of a pre-ergocalciferol solution with light of wavelength >310 mμ. According to the results, represented in Figs. 2 and 3, the photochemical conversion of pre-ergocalciferol yields more than 90 per cent tachysterol$_2$ and about 5 per cent ergosterol as primary products.[3] In the same way it was established that tachysterol$_2$ gives 70 per cent pre-ergocalciferol and no detectable amount of ergosterol, the balance probably consisting of lumisterol$_2$. Lumisterol$_2$ yielded 100 per cent pre-ergocalciferol.[4] Ergosterol was converted to the extent of 85 per cent into pre-ergocalciferol and 15 per cent into other products ("over-irradiation products"?, not lumisterol$_2$).[5]

Quantum yields were determined for the photoconversions of the four isomers using radiation of $\lambda = 2537$ Å.[5] The results lead to the reactions represented in Fig. 4.

On account of its experimental basis the scheme, Fig. 4, may prove to be fairly definite with respect to its major lines. The chief remaining uncertainties are related to the reactions that may lead to lumisterol. As small amounts of this compound are difficult to determine, it is planned to tackle these problems with the aid of tracer

[2] L. Velluz, G. Amiard and A. Petit, *Bull. Soc. Chim. Fr.* 501 (1949); L. Velluz, G. Amiard and B. Goffinet, *Ibid.* 1341 (1955).
[3] M. P. Rappoldt, *Rec. Trav. Chim.* In press.
[4] M. P. Rappoldt, *Rec. Trav. Chim.* 79, 392 (1960).
[5] M. P. Rappoldt and E. Havinga, *Rec. Trav. Chim.* 79, 369 (1960).
[6] M. P. Rappoldt, J. A. Keverling Buisman and E. Havinga, *Rec. Trav. Chim.* 77, 327 (1958).

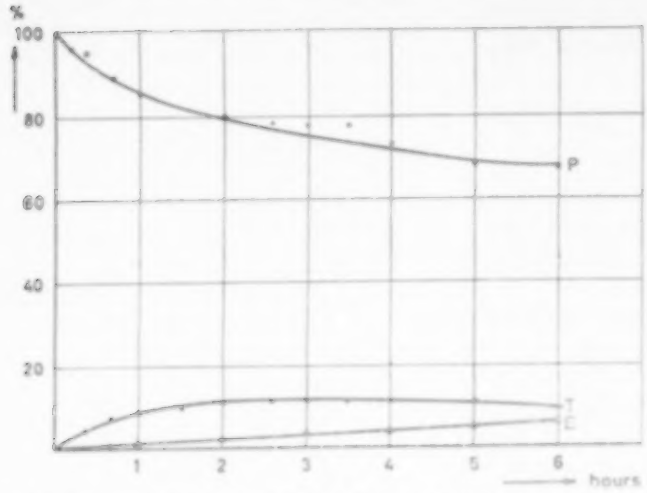

FIG. 2. Irradiation of a pre-ergocalciferol solution with light of wavelength > 310 mμ. Percentages of P, T and E in the solute plotted against the irradiation time.

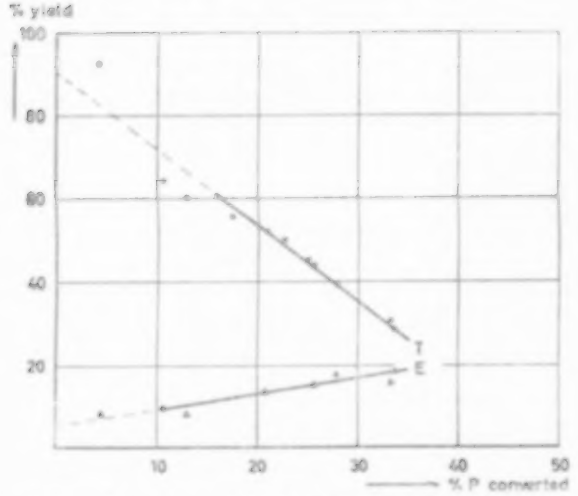

FIG. 3. Irradiation of a pre-ergocalciferol solution with light of wavelength > 310 mμ. Percentages of T and E in the conversion product plotted against percentages of P converted.

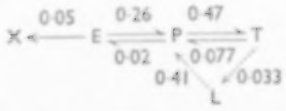

FIG. 4. The essential photochemical reactions of ergosterol and its isomers with quantum yields at 2537 Å.

experiments. In accordance with the view expressed in an earlier paper,[6] the excited states of the various isomers, formed by absorption of light, appear to differ from each other. This is especially noteworthy in the case of the *cis*/*trans* isomers P and T; on photoactivation, these compounds undergo—besides interconversion—ring closure

to form different products (E and L, respectively). Later in this paper, the mechanistically important difference between excited *cis* and *trans* isomers, also observed in the case of stilbene,[7] is referred to.

(b) *The photostationary state*

If the scheme represented in Fig. 4 is correct, prolonged irradiation should give rise to a quasi-stationary state. For a given wavelength the composition of this state would

TABLE 1. PERCENTAGES OF P, T AND E IN THE SOLUTE AFTER PROLONGED IRRADIATION, $\lambda = 2537$ Å

Starting material	% in the solute		
	T	P	E
Ergosterol	68	14	
Tachysterol$_2$	72·5	15·5	1·4
Lumisterol$_2$	71	14·5	1·5

TABLE 2. THE CALCULATED COMPOSITION OF THE PHOTOSTATIONARY STATE AT VARIOUS WAVELENGTHS

λ in mμ	% E	% P	% T	% L
253·7	2	19	68	11
280	1·5	47	41	10
296·5	1·4	60	27	12
302	3·4	53	26	17
313	26	19	8	47

be the same, irrespective of the isomer used as starting material. The formation of "over-irradiation" products does not give rise to serious complications; it proceeds slowly enough to assure constant concentration during a considerable period. Ergosterol, tachysterol$_2$ and lumisterol$_2$ were irradiated with light of wavelength 2537 Å until constant concentration was reached; the results of these experiments are summarized in Table 1. The same stationary state is reached by prolonged irradiation of each of the isomers considered.

The data represented in Fig. 4, together with the extinction coefficients of the various isomers at a given wavelength, enable us to predict by calculation the composition of the (quasi) photostationary state at that wavelength. Adhering to the assumption that the quantum yields do not vary appreciably within the wavelength region (250–320 mμ) concerned, the results represented in Table 2 were obtained for the composition of the stationary state mixtures at varying wavelengths. These figures have only semiquantitative value.

The first conclusion to be drawn from the figures is, within the limits of error, that there is agreement with the experimental data obtained with $\lambda = 2537$ Å (Table 1). This supports the validity of the scheme, Fig. 4, and the assumption of the constancy of the stoicheiometric pattern with varying wavelength that formed the basis of the evaluation leading to Table 2. It must be pointed out, that whereas quantum yields of

[7] G. Riezebos, Thesis, Leiden (1959).

conversion were measured at 2537 Å, the stoicheiometric yields of formation of the various reaction products were mostly determined at longer wavelengths.

Table 2 clarifies the situation with respect to the seemingly contradictory remarks in the literature about the yields of photo-products. Harris *et al.*[8] reported that "the photochemical activation of ergosterol by ultra-violet light of 2537–3025 Å is substantially uniform per quantum of energy applied". It has been reported that light of 270–310 mμ gives a high yield of vitamin D, light of shorter wavelength yields mainly tachysterol and light of longer wavelength causes production of predominantly lumisterol.[9] The data of Table 2 demonstrate clearly the shift in the yields of products to be expected from long-term irradiation experiments with light of varying wavelengths.

(c) *Some investigations into the nature of the photochemical intermediates*

While the knowledge of the paths of reaction and of the stoicheiometry of the photo-isomerizations in the vitamin D field has substantially increased in recent years, the study of the reaction mechanisms is still in the orientation stage. In a previous publication,[10] it was mentioned that there is the possibility that illumination of provitamin D (and other isomers) may give rise to a triplet state that could function as a not too short lived intermediate. Efforts have been made to investigate this possibility. With this in mind, the luminescence spectra were measured. During irradiation of solid solutions of ergosterol or 7-dehydrocholesterol in EPA* at 80°K, no indications of phosphorescence were found. From these experiments, the occurrence of bi-radicals or triplet states seems rather improbable. Solutions of ergosterol in EPA or ether showed no luminescence upon irradiation at room temperature with ultra-violet light of $\lambda = 230$–300 mμ. As the quantum yield of the photochemical conversion of ergosterol in ethereal solution is about 0·3, 70 per cent of the excited ergosterol molecules seem to lose, under these conditions, their surplus energy by radiationless transitions. Characteristic fluorescence was, however, observed during illumination of solid solutions in EPA of ergosterol, lumisterol and tachysterol and also of pyrocalciferol (9α-lumisterol) and isopyrocalciferol (9β-ergosterol). The shape of the spectra (cf. Fig. 5, 6, 7 and 8), having mirror symmetry with the corresponding ultra-violet absorption spectra, together with other criteria, identify these fluorescence spectra as due to transitions from the lowest level of the first excited singlet state to the lower levels of the ground state. It should be noticed that the *cis* isomer pre-ergocalciferol does not show fluorescence nor phosphorescence.

On the evidence now available, it would appear that the photo-isomerizations of the pro- and pre-vitamins D occur via the excited singlet states of the various molecules. In order to arrive at a more positive conclusion, it is necessary to know both the quantum yields of the photochemical conversions and the fluorescence yields obtained with solid solutions (at $\sim$ 80°K).

(d) *Discussion*

It is not difficult to conceive that in the excited singlet state the atoms 9 and 10 of

* A mixture of 5 parts ether, 5 parts isopentane and 2 parts ethanol.

[8] R. S. Harris, J. W. M. Bunker and L. M. Mosher, *J. Amer. Chem. Soc.* **60**, 2579 (1938).

[9] E. H. Reerink and A. van Wijk, *Strahlentherapie* **40**, 728 (1931); A. Windaus, K. Dithmar and E. Fernholz *Liebigs Ann.* **493**, 259 (1932); Cf. H. Vogel and H. Knobloch, *Chemie und Technik der Vitamine* p. 218. Ferdinand Enke Verlag, Stuttgart (1950).

[10] E. Havinga, A. Verloop and A. L. Koevoet, *Rec. Trav. Chim.* **75**, 371 (1956).

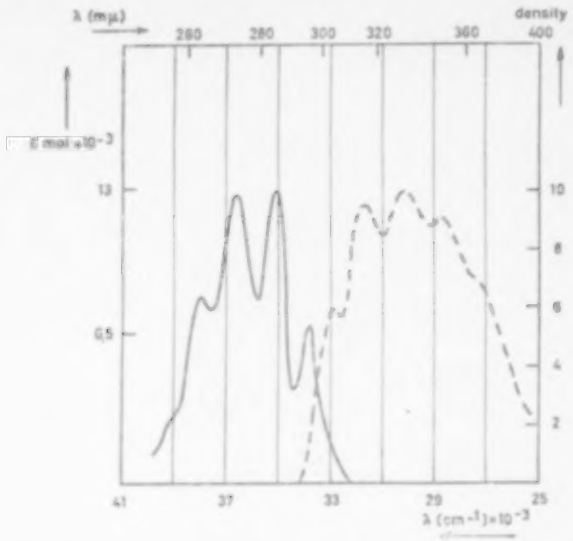

FIG. 5. —— Ultra-violet absorption spectrum of ergosterol at 80°K. – – – – Fluorescence spectrum of ergosterol in EPA at 80°K.

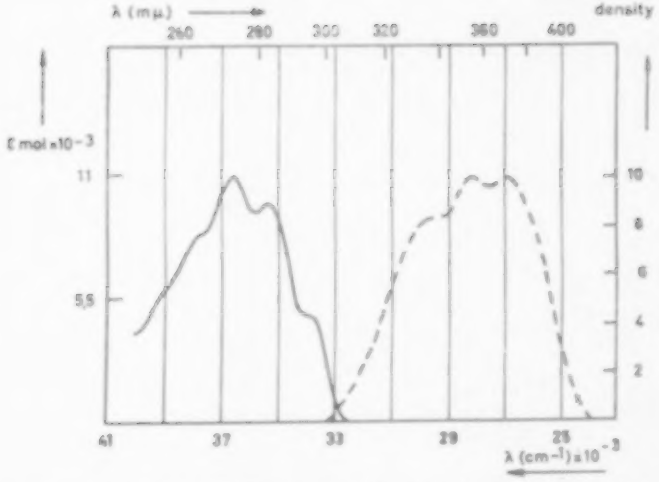

FIG. 6. —— Ultra-violet absorption spectrum of lumisterol$_2$ at 80°K. – – – – Fluorescence spectrum of lumisterol$_2$ in EPA at 80°K.

ergosterol or lumisterol$_2$ can move away from each other smoothly without passing through a highly unfavourable state at any time. The molecule will thus transform into the open *cis*-hexatriene derivative (pre-ergocalciferol).

This ring opening constitutes one of the main photochemical reactions occurring with 1,3-cyclohexadiene systems and also occurs with α-phellandrene and 1,3-cyclohexadiene.[11] The reverse reaction, i.e. the ring closure of excited hexatriene derivatives,

[11] R. J. de Kock, N. G. Minnaard and E. Havinga, *Rec. Trav. Chim.* **79**, 922 (1960); cf. R. J. de Kock, Thesis Leiden (1959); D. H. R. Barton, *Helv. Chim. Acta* **42**, 2604 (1959); R. Srinivasan. Personal communication.

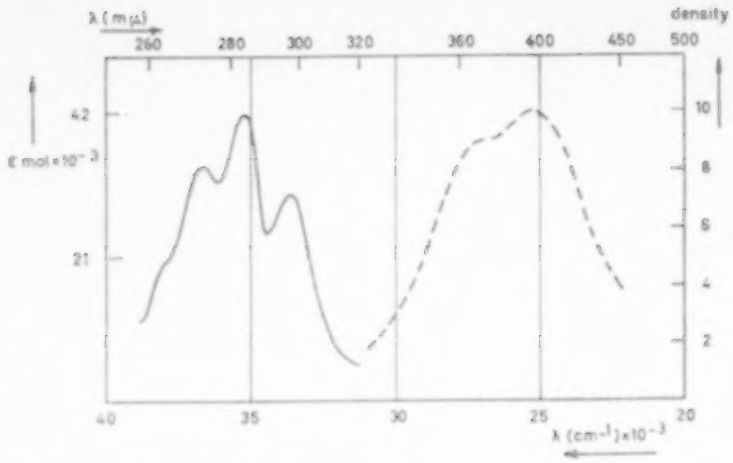

FIG. 7. —— Ultra-violet absorption spectrum of tachysterol$_2$ at 80°K. - - - - Fluorescence spectrum of tachysterol$_2$ in EPA at 80°K.

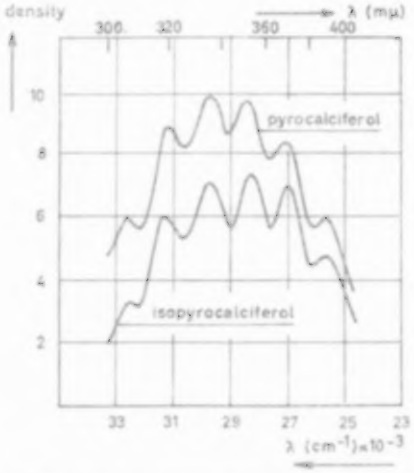

FIG. 8. Fluorescence spectra of pyro- and isopyro-calciferol.

seems to offer no special difficulties from a mechanistic point of view. It remains to be explained, however, why pre-ergocalciferol undergoes photo-induced ring closure into ergosterol whereas tachysterol$_2$ seems to be transformed preferentially into lumisterol$_2$. Further stereochemical specificities that offer problems with regard to mechanistic concepts, are found in the result of a special investigation that established the absence of the stereoisomers pyro- and isopyro-calciferol in the reaction mixture obtained by irradiation of an ethereal solution of ergosterol for a long time (see Experimental). Evidently, photochemical ring closure of pre-ergocalciferol and tachysterol] leads exclusively to ergosterol and lumisterol$_2$ (9, 10 anti-isomers) whereas the thermal ring closure of (pre)vitamin D$_2$ results specifically in the pyro- and isopyro-calciferols (9, 10 syn-isomers). It is remarkable that lumisterol$_2$ photo-isomerizes quantitatively into

pre-ergocalciferol while ergosterol forms some 15 per cent of another, still unidentified product. Finally, it may be remarked that pyro- and isopyro-calciferol show ultra-violet absorption and fluorescence spectra that are similar to those of ergosterol and lumisterol. The pyro-compounds undergo photo-isomerization, in which the cyclohexadiene B ring is transformed into a bicyclic system.[12] The photochemical *cis/trans* isomerization, pre-ergocalciferol ⇆ tachysterol$_2$, also shows some remarkable aspects.*

Extrapolation of the conclusions drawn from the energies calculated for the various conformations and configurations of the ground states and the first excited states in the case of *trans* and *cis* stilbene,[7] leads one to expect that the sterically hindered pre-ergocalciferol, upon being excited by the uptake of a light quantum, would be able to transform into the energetically more favourable *trans* conformation. This "down hill" movement would need no extra thermal activation. Thermal energy remains necessary for the conversion of the excited *trans* form into the *cis* conformation with probably a few kilocalories higher energy content. It was found, contrary to what happens at room temperature, that the *trans* compound tachysterol$_2$ is not isomerized into pre-ergocalciferol by irradiation at 80°K, either in solid solution in EPA or in liquid solution in propane. The *cis*→*trans* isomerization, on the other hand, still occurs at 80°K even in solid solution. It thus appears that the pattern of the photo-interconversion of pre-ergocalciferol and tachysterol$_2$ is consistent with results obtained in the study of other *cis/trans* isomers, that of stilbenes in particular. With pre-ergocalciferol and tachysterol$_2$ the difference between the photo-excited *cis* and *trans* isomers is particularly evident from the difference of their chemical transformations.

EXPERIMENTAL

The photostationary state

A solution of 1·0 g ergosterol in 2 l. ether was irradiated with ultra-violet light of wavelength 2537 Å. This radiation was obtained from a low-pressure mercury vapour lamp (Philips TUV 15 Watt), the light of which was filtered by 1 cm of gaseous chlorine at 2 atm press. The temp was kept between 10° and 20°. Samples taken at irradiation times of 3, 3½ and 4 hr contained equal amounts of pre-ergocalciferol and tachysterol$_2$. The irradiation technique and the analytical methods have been described elsewhere.[5] Similar experiments were carried out with lumisterol$_2$ and tachysterol$_2$ as starting materials. The values of the concentrations found at the irradiation times mentioned were averaged and expressed as percentages of the solute. The results are summarized in Table 1.

The calculated composition of the (quasi) photostationary state to be expected at various wavelengths started from the following equations:

$$E + P + T + L = 100$$

$$\frac{T}{P} = \frac{0{\cdot}47}{0{\cdot}077 + 0{\cdot}033} \times \frac{\varepsilon P}{\varepsilon T}$$

$$\frac{T}{L} = \frac{0{\cdot}41}{0{\cdot}033} \times \frac{\varepsilon L}{\varepsilon T}$$

$$\frac{P}{E} = \frac{0{\cdot}26 + 0{\cdot}05}{0{\cdot}002} \times \frac{\varepsilon E}{\varepsilon P}$$

εP, εT, εL, and εE are the extinction coefficients. In Table 3 the $E_{1cm}^{1\%}$ of P, T, L and *E* is given at the wavelengths used.

* We wish to thank Prof. Dr. L. J. Oosterhoff and Dr. G. Riezebos for valuable discussions.

[12] A. Windaus, K. Dimroth and W. Breywisch, *Liebigs Ann.* **543**, 240 (1940); W. G. Dauben and G. J. Fonken, *J. Amer. Chem. Soc.* **81**, 4060 (1959).

The absence of pyro- and isopyro-calciferol in irradiation mixtures

A solution of 9 g ergosterol in 4 l. ether was irradiated for 9 hr with the unfiltered light of a high-pressure mercury vapour lamp (Philips HOV 1500 watt). The temp of the solution was kept between 10° and 20°. After removal of the solvent, a resinous product with weak ultra-violet absorption was obtained. $\lambda_{max} = 243$ mμ; $E^{1\%}_{1\,cm} = 80$. Heating of the resin for 1 hr at 200° or at 300° caused a slight increase of the extinction, but no maxima near 270 and 280 mμ developed. These maxima would be expected if an appreciable amount of photo-pyrocalciferol or photo-isopyrocalciferol had been present in the irradiation product. Therefore it may be concluded that pyro- and isopyro-calciferol are not formed by irradiation of ergosterol or of its photo-isomers. This conclusion is not justified in the hypothetical case that photo-pyro- and isopyro-calciferol are intermediates in the formation of "over-irradiation products".

TABLE 3. SPECIFIC EXTINCTIONS OF ERGOSTEROL AND ITS ISOMERS

λ in mμ	$E^{1\%}_{1cm}$ (ether)			
	E	P	T	L
253·7	121	207	250	120
280	295	141	705	226
296·5	132	48	463	82
302	28	28	245	30
313	0·4	8·6	90	1·2

Measurement of the ultra-violet absorption and luminescence spectra at 80° K

(a) The ultra-violet absorption spectra were measured in a specially designed cell which was similar to the one described by Potts[13]. The solvent was a mixture of 3 parts isopentane and 1 part methylcyclohexane.

(b) The luminescence was achieved by means of a super-high-pressure mercury vapour lamp (Philips SP 500 watt). The light of this lamp passed successively through a 2 cm layer of a solution of 60 g $NiSO_4.7H_2O$ and 20 g $CoSO_4.7H_2O$ in 100 ml water, a 3 cm layer of gaseous chlorine and a Corning Filter No 9863. This filter combination removed all incident radiation above 300 mμ.

The solutions to be studied were placed in a cylindrical quartz tube, immersed in an unsilvered Dewar vessel filled with liquid air. The solvents used were EPA (a mixture of 5 parts ether, 5 parts isopentane and 2 parts ethanol) and MIP (a mixture of 1 part methyl cyclohexane and 3 parts isopentane).

Phosphorescence was measured according to the method described by van Roggen and Vroom[14] using rotating shutters. In the fluorescence experiments the exciting light fell on the sample perpendicularly to the direction in which the emission was measured.

A quartz lens placed behind the sample condensed the luminescence light on the slit of a Hilger medium quartz spectrograph. The spectra were recorded by means of Ilford HPS plates or, when infra-red emission was investigated, with Kodak IL plates.

[13] W. J. Potts, *J. Chem. Phys.* **21**, 191 (1953).
[14] A. van Roggen and R. A. Vroom, *J. Sci. Instrum.* **32**, 180 (1955).

Tetrahedron, 1960, Vol. 11, pp. 285 to 289. Pergamon Press Ltd. Printed in Northern Ireland

INFRA-RED INTENSITY MEASUREMENTS ON DIAZOCOMPOUNDS

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Abstract—Integrated intensities and frequencies are given for the diazo and carbonyl bands of a few aromatic diazohydrocarbons and *p*-substituted diazoacetophenones. The results, compared with previous related infra-red and photochemical data, are discussed in terms of the relevant resonance structure in the different cases. Tentative arguments are given for a possible assignment of the >CNN grouping symmetrical stretching mode, apparently strongly coupled to the carbon skeletal of the molecule.

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THE spectroscopical and photochemical study of diazocompounds has recently been developed. In the case of diazomethane[1] the vibrational spectra have been well investigated and interpreted but this investigation for diazohydrocarbons and diazoketones is limited to the stretching frequencies of NN and CO groupings[2] and to the study of possible interactions with solvent medium.[3] The electronic spectra appear to have been examined[4] only at an introductory level, mainly in connexion with photochemical measurements, which on the other hand have given interesting information concerning structural influences on the quantum yield of the photolysis and the reactivity of the carbene fragments produced in the primary photolytic act, both in ordinary conditions[5] and in a matrix.[6] In connexion with spectroscopic–photochemical and electrochemical[7] investigation on diazocompounds, we have given some results of frequency and intensity measurements on the NN and CO stretching bands for a few simple diazohydrocarbons and for *p*-substituted diazoacetophenones; a vibrational study for a few parent molecules of this group, particularly diazocyclopentadiene and diazoacetone, is in progress.

EXPERIMENTAL

A Perkin–Elmer Model 112 spectrometer with CaF_2 optics was used throughout; the NaCl cells had a thickness of 0·121 and 1·000 mm. The data in Table 1 are for CCl_4 soln unless otherwise noted, those in Table 2 for CCl_4 soln in the case of NN and ω_3 bands, for C_2Cl_4 soln in the case of CO band; CCl_4 and C_2Cl_4 were purified by reflux over P_2O_5 and K_2CO_3 respectively, and distillation. The frequency values for the 4·8 μ, range now obtained are on an average 15 cm^{-1} higher than those reported by Yates and Shapiro[2a], the difference being due to better experimental conditions with a

[1] B. L. Crawford, W. H. Fletcher and D. A. Ramsay, *J. Chem. Phys.* **19**, 406 (1951); W. H. Fletcher and T. P. Garrett, *Ibid.* **25**, 50 (1956); J. M. Mills and H. W. Thompson, *Trans. Faraday Soc.* **50**, 1270 (1954).
[2] [a] P. Yates and L. B. Shapiro, *J. Amer. Chem. Soc.* **79**, 5756 (1957); [b] E. Fahr, *Liebigs Ann.* **617**, 11 (1958); [c] H. N. Beck, *Diss. Abstr.* **18**, 1250 (1958).
[3] [a] E. Fahr, *Chem. Ber.* **92**, 398 (1959); [b] F. A. Miller, *J. Amer. Chem. Soc.* **79**, 5974 (1957).
[4] A. J. Ultée and J. B. J. Soons, *Rec. Trav. Chim.* **71**, 565 (1952); G. Kortum, *Z. Phys. Chem.* **50**, 379 (1941).
[5] W. Kirmse, L. Horner and H. Hoffmann, *Liebigs Ann.* **614**, 19 (1958); W. Kirmse and L. Horner, *Ibid.* **625**, 34 (1959).
[6] G. Pimentel, D. E. Milligan and T. D. Goldfarb, *J. Chem. Phys.* **29**, 1405 (1958); *J. Amer. Chem. Soc.* **82**, 1865 (1960); G. W. Robinson and M. McCarty, Jr., *Ibid.* **82**, 1859 (1960); W. B. De More and N. Davidson, *Ibid.* **81**, 5869 (1959).
[7] A. Foffani, L. Salvagnini and C. Pecile, *Ann. Chim. Ital.* **49**, 1677 (1959).

more efficient standardization through the 4·6 μ CO band. The data here reported are, therefore, more accurate than the previous ones, with an estimated accuracy of ± 2 cm^{-1}.

The integrated intensities, in units mole^{-1} litre cm^{-2}, were measured with the Wilson–Wells method as previously described;[8] the estimated spectral slit-width was 5·4–4·1 cm^{-1}. The integration was extended over an interval of about 100 cm^{-1}, the overlapping with neighbouring bands often being negligible and, when necessary, being corrected for graphically. The concentration of the solutions was in the range $5 \cdot 10^{-2}$–$3 \cdot 10^{-2}$ moles/litre for the NN band, $8 \cdot 10^{-2}$–$6 \cdot 10^{-2}$ moles/litre for CO band. At least four independent intensity determinations were performed on any band of any single compound. All compounds were carefully purified during preparation.[9]

RESULTS AND DISCUSSION

Tables 1 and 2 give frequency, integrated intensity and half-width values for the NN and CO stretching bands of the compounds examined. As only limited information is available concerning the assignment of bands in the spectra of diazocompounds other than diazomethane, it was of interest to examine first the possible position of the (pseudo)-symmetrical stretching mode of the >CNN triatomic group which characterizes these compounds. In the following footnote* the average frequency ranges are given for other organic molecules with triatomic group vibrationally correlated to diazocompounds, implying a (pseudo)-asymmetrical stretching frequency located in the range characteristic of triple bonds or of cumulated double bonds. In the case of diazomethane this is correctly assigned at 852 cm^{-1},[1] but for other aliphatic diazohydrocarbons there is no indication, while the spectra for aromatic diazohydrocarbons do not indicate a reliable position.

On the other hand, diazoketones[2] and diazoesters show a strong band at 1335–1410 cm^{-1}, not observed in diazohydrocarbons with the exception of diazocyclopentadiene[12a] which shows a strong band at about 1300 cm^{-1} not present in cyclopentadiene.[12b] Such a band can not correspond to a CH deformation mode for monosubstituted diazoketones, as it is also observed in the disubstituted compounds. In addition the carbonyl skeletal vibration ($\nu_4 = 1225$ cm^{-1} for acetone[13]) and the ω_3 aromatic ring mode should be assigned to a lower frequency interval, falling for example around 1255 cm^{-1} for acetophenones and most probably, around 1225 cm^{-1} for diazoacetophenones, with shape and intensity clearly different from those of the band being discussed (see below). These arguments seem to support the possible

* RN_3, $RCON_2$, 1340–1180 cm^{-1}; RNCO, ~1350 cm^{-1}; RNCS, RSCN, ~680 cm^{-1}; allene, 1070 cm^{-1}; CH_2CO, 1124 cm^{-1}.[10] Additional examples may be drawn from data available also for triatomic molecules and inorganic anions: CN_2^{2-}, 1234 cm^{-1}; SCO, 859 cm^{-1}; NCS^-, 750 cm^{-1}; NCO^-, 1300 cm^{-1}; N_3^-, 1344 cm^{-1} and so forth.[11]

[8] A. Foffani, C. Pecile and F. Pietra, *Nuovo Cimento* **13**, 213 (1959); D. A. Ramsay, *J. Amer. Chem. Soc.* **74**, 72 (1952).

[9] $C_6H_5CHN_2$: A. Hantzsch and M. Lehmann, *Chem. Ber.* **35**, 897 (1902); $C_6H_5CN_2$: L. I. Smith and K. L. Howard, *Organic Syntheses* Coll. Vol. III, p. 351 (1955); $C_6H_5COC(C_6H_5)N_2$: C. D. Nenitzescu and E. Solomonica, *Ibid.* Coll. Vol. II, p. 496 (1943); CH_3COCHN_2: F. Arndt and J. Amende *Chem. Ber.* **61**, 1122 (1928); Diazoacetophenones: A. L. Wilds and A. L. Meader, *J. Org. Chem.* **13**, 763 (1948); W. Bradely and G. Schwarzenbach, *J. Chem. Soc.* 2904 (1928); L. Canonica, *Gazz. Chim. Ital.* **80**, 412 (1950); Diazocyclopentadiene: W. von E. Doering and C. H. De Puy, *J. Amer. Chem. Soc.* **75**, 5955 (1953).

[10] Yu. N. Shcinker and Ya. K. Syrkin, *Izv. Akad. Nauk SSSR, S.F.* **14**, 478 (1950); N. S. Ham and J. B. Willis, *Spectrochim. Acta* **16**, 279 (1960); J. Lecomte, *Handbuch der Physik* Band XXVI, pp. 595, 499, 409. Springer, Berlin (1958); J. Goubeau and J. Reyhing, *Z. Anorg. Chem.* **294**, 96 (1958).

[11] S. K. Deb and A. D. Yoffe, *Trans. Faraday Soc.* **55**, 106 (1959); J. Lecomte, *loc. cit.* pp. 747, 748; T. C. Waddington, *J. Chem. Soc.* 2500 (1959); P. Gray and T. C. Waddington, *Trans. Faraday Soc.* **53**, 901 (1957).

[12a] W. von E. Doering and C. H. De Puy, *loc. cit.*; [b] American Petroleum Institute research Project 44, National Bureau of Standards (U.S.A.) Catalog of Infra-red Spectral Data, serial N. 458; J. Lecomte, *Bull. Soc. Chim.* **13**, 415 (1946).

[13] S. A. Francis, *J. Chem. Phys.* **19**, 942 (1951).

assignment of the band 1300–1400 cm^{-1} to the symmetrical stretching mode of >CNN grouping, strongly raised in its frequency for compounds showing a high degree of conjugation implying a relevant electron shift from diazogroup and an increasing degree of coupling of the triatomic >CNN grouping to the skeletal of the molecule, giving this symmetrical mode a higher character of skeletal mode. In order to clarify this problem, a structural study is clearly necessary.

TABLE 1. DIAZOHYDROCARBONS AND DIAZOKETONES

Compounds	ν_{NN} cm^{-1}	$A_{NN} \times 10^{-4}$	$\Delta\nu_{1/2}$	ν_{CO} cm^{-1}	$A_{CO} \times 10^{-4}$	$\Delta\nu_{1/2}$
CH_2N_2	2088[a]					
$CHC_6H_5N_2$	2062	4·2				
$CC_6H_{12}N_2$	2042	7·3[b]				
Diazocyclopentadiene	2089	5·8				
CH_2COCHN_2	2107[a]	3·7[b][a]		1659	2·8	15
$C_6H_5COCHN_2$	2108	5·8[b]	14	1633	1·8	11
$C_6H_5COC(C_6H_5)N_2$	2072	5·4[b]	14	1636	2·7	14
$C_2H_5OOCCHN_2$	2117[c]			1695[c]		

[a] Ethereal soln.; [b] Corrected for the contribution of a weaker band at 2090 cm^{-1}; [c] from Yates[26]; ν_{NN} corrected by + 16 cm^{-1} (see Experimental).

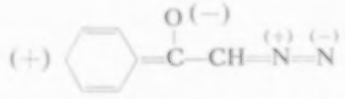
TABLE 2. DIAZOACETOPHENONES[a]

X—C_6H_4—CO—R	R = CHN_2							R = CH_2[b]		
	ν_{NN} cm^{-1}	$A_{NN} \times 10^{-4}$	$\Delta\nu_{1/2}$	ν_{CO} cm^{-1}	$A_{CO} \times 10^{-4}$	$\Delta\nu_{1/2}$	ω_3 cm^{-1}	ν_{CO} cm^{-1}	$A_{CO} \times 10^{-4}$	ω_3[d] cm^{-1}
X = *p*-OCH_3	2103	6·0	11	1631	2·4	12	1227	1682	2·1[c]	1258 *l*
p-CH_3	2108	5·4	12	1634			1278	1687	2·4[c]	1265 *s*
p-H	2108	5·8[c]	14	1634	1·8[c]	10	1223	1691	2·2[c]	1260 *s*
p-Cl	2109	4·6[c]	13	1632	2·0[c]	13	1218	1692	2·2[c]	1259 *l*
p-NO_2	2112	5·4[c]	14	1642	1·6[c]	13	1215	1700	1·9[c]	1238 *s*

[a] Data for NN and ω_3 band as CCl_4 soln, for CO band as C_2Cl_4 soln; [b] see[15]; [c] as $CHCl_3$ soln[14]; [d] *l* = liq. *s* = solid.[16]

In this connexion it may be mentioned that similar frequency shifts of the asymmetrical vibration[2] have been observed. In the case of aliphatic diazohydrocarbons there is a gradual frequency decrease of this band by increasing the number of substituents at carbon, independent in a first instance of the type of substituent. The aromatic diazohydrocarbons behave similarly, apparently through some kind of compensation of the effects of the two structures due to diazogroup–aromatic ring conjugation with either positive or negative charge at the *para* carbon atom. This is also supported by the high frequency value of the >CNN asymmetrical stretching mode for diazocyclopentadiene (2089 cm^{-1}, to be compared with the corresponding average figure 2040 cm^{-1} for disubstituted aromatic diazohydrocarbons), where such a competitive effect of conjugated structures is not operative, there being only the strong mesomeric electron donating effect of diazogroup towards the cyclopentadiene ring, apparently owing to the prevalence of a structure of the type $C_5H_4^{(-)}—N^{(+)}\equiv N$. Presumably this effect might cause for this molecule, as distinct from aromatic diazohydrocarbons,[5] a relevant lowering of the quantum yield for the photolysis.

In aliphatic α-diazocarbonyl compounds containing the same number of substituents, a single α-carbonyl causes a frequency increase of the >CNN asymmetrical stretching mode by an average of 40 cm^{-1}, through the intervention of a structure of type: $R-\overset{\overset{O(-)}{|}}{C}=CH-\overset{(+)}{N}=N$ involving diazogroup–carbonyl conjugation; the effect is further enhanced by addition of a second α-carbonyl group. It is of interest to note, that in diazoacetone and diazoacetophenone (see Table 1), although aromatic substitution does not appreciably effect the >CNN asymmetrical stretching mode frequency, it lowers the corresponding carbonyl stretching frequency by 25 cm^{-1}, a lowering almost equal to the 24 cm^{-1} observed in acetone and acetophenone. This is due to the intervention of the normal carbonyl–phenyl conjugative structure, which in this case is of the type:



involving on diazo-band a partial compensation of the diazo–carbonilic conjugative effect, while enhancing this very effect on the carbonyl stretching frequency, with an additional contribution for an amount almost equal to the one observed for other conjugated carbonyl compounds. Similarly the quantum yield of the photolysis[5] is lowered by about 0·2 units on going from diazobutanone to diazoacetophenone.

The parallelism ketones–diazoketones as to aryl-substitution is also reflected on the substituent effects to aromatic ring on the carbonyl stretching frequency, which are in the same direction and of the same order of magnitude for the frequency as well as for the intensity (see Table 2), although the effect on the intensity is very small.* Other couples which may be compared are for example ethyl acetate–ethyl benzoate and phenyl acetate–phenyl benzoate, with carbonyl frequency lowerings 22 and 25 cm^{-1} respectively and similar *p*-substitution effects on frequency and intensity.[14a,b] In this connexion it may be noted that the quantum yield for the photolysis of diazoacetophenone shows[5] a tendency to decrease for every type of *ortho*- or *para*-substitution, an effect not yet understood.

As to the absolute values of the intensities it may be observed instead that for diazoacetone and diazoacetophenone the aryl-substitution causes a strong intensity decrease for 1 $mole^{-1}$ litre cm^{-2}, compared[14a,b] with an increase of about 0·5 units for the couple acetone–acetophenone, while for the couples ethyl acetate–ethyl benzoate and phenyl acetate–phenyl benzoate there are only small variations, which are within the limits of experimental error. The apparently anomalous effect on the intensity of carbonyl band is probably due to the strong mesomeric effect of the diazo group, as is reflected in the exceptionally low value of the carbonyl frequency for the compounds†

* Table 2 reports also the frequency of the band at 1215–1230 cm^{-1} for the *p*-substituted diazoacetophenones, compared with the one at 1240–1265 cm^{-1} for the acetophenones; as before mentioned, the intensity and shape of the two bands, their position and the parallel trend of the substituent effect strongly support their common assignment to the ω_3 aromatic ring in-plane skeletal mode, well known for being substituent sensitive and which in the present case perhaps is also partaking, at least partially, the character of the carbonylic skeletal mode (ν_4 = 1225 cm^{-1} for acetone) falling in the same range.

† For example: ν_{CO} (acetone)–ν_{CO}(diazoacetone) = 56 cm^{-1}; ν_{CO}(acetophenone)–ν_{CO}(diazoacetophenone) = 57 cm^{-1}; ν_{CO}(ethyl acetate)–ν_{CO}(ethyl diazoacetate) = 47 cm^{-1}.

[14a] H. W. Thompson and D. A. Jameson, *Spectrochim. Acta* **13**, 236 (1958); [b] *Ibid.* **9**, 208 (1957); [c] R. N. Jones, *Canad. J. Chem.* **35**, 504 (1957); [d] B. P. Susz and P. Chalandon, *Helv. Chim. Acta* **41**, 1338 (1958).

and in the particularly high value of the frequency of the >CNN asymmetrical stretching mode for diazocyclopentadiene. Trichloro and trifluoro-diazoacetone[2c,15] are unusual due to the superposition of the strong inductive effect of the $—CHCl_3$ grouping, the carbonyl band shift being 80 cm^{-1} for CCl_3COCH_3 and CCl_3COCHN_2 and 112 cm^{-1} for the trifluoro-derivatives.

As to the intensity of the >CNN grouping asymmetrical stretching mode in diazohydrocarbons and diazocarbonyl compounds, the situation appears to be more involved and difficult to interpret due to the limited data presently available. There seems to be a rough parallelism with the characteristic structural effects on the frequency, with a strong influence of the substitution at carbon atom on the degree of coupling within the >CNN grouping: the intensity increases strongly on going from phenyl- to diphenyl-diazomethane but the behaviour of diazocarbonyl compounds is less clear, presumably owing to the competitive action of carbonyl–phenyl conjugation, difficult to evaluate in its effect on the diazoband intensity.

[16] L. J. Bellamy and R. L. Williams, *J. Chem. Soc.* 4304 (1957).

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BOOK REVIEW

F. CHALLENGER: **Aspects of the Organic Chemistry of Sulphur.** Butterworth's Scientific Publications, London, 1959. vii + 253 pp., £2, $7.50.

PROFESSOR CHALLENGER is well qualified to write a book on the organic chemistry of sulphur, for this has been his primary interest throughout a long chemical career. Six very different topics are dealt with in separate chapters.

Chapter 1 deals with simple organic compounds containing sulphur and gives the general reader a broad picture of properties, preparations and the biological significance of a wide range of substances. The next chapter gives useful information on natural sulphonium compounds, sulphides, sulphoxides, mercaptans and sulphido-amino acids. For example, an account is given of the toxic principle produced in flour which has been treated with traces of nitrogen chloride vapour in order to improve the baking properties. The toxic factor arises from the action of the nitrogen trichloride (agene) on the protein gluten contained in the wheaten flour. The treated protein on hydrolysis gives the previously unknown methionine sulphoximine

Among other topics discussed are the sulphur compounds of asparagus which are alleged to be responsible for the odour of urine after the ingestion of asparagus.

The third chapter deals adequately with the sulphur compounds of petroleum and other mineral oils and various aspects of desulphurization processes are considered.

A useful chapter is devoted to oil of mustard and an account is given of early work dating back to 1608.

The fifth chapter concerns biological methylation with particular reference to compounds of sulphur. Here we learn a great deal about the author's own contributions to the subject and these have been extensive since 1931. The part played by methionine in transmethylations is explained and the work of du Vigneaud in this connexion is given prominence. This chapter closes with speculations on the mechanisms of the antitubercular effect of ethanethiol in animals.

As might be guessed, no book on organic sulphur compounds would be complete with outsome account of Co-enzyme A, its acetyl derivative and related compounds. Accordingly the last chapter is devoted to these topics.

This book is very readable and Professor Challenger has done good service by bringing together in one quite small volume a number of topics concerning the organic chemistry of sulphur which might otherwise appear unconnected. He has been successful in getting the right balance: he does not overload his reader with detail, but stimulates him sufficiently to be anxious to look up some of the many references given at the end of each chapter.

B. C. SAUNDERS

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A list of some of the papers to be published in future issues

M. I. KABACHNIK, S. T. IOFFE, E. M. POPOV and K. V. VATSURO: *Trans*-enolization.

N. K. KOCHETKOV, L. J. KUDRYASHOV and B. P. GOTTICH: Ketovinylation of β-dicarbonyl compounds.

B. D. PEARSON: The electronic spectra of the nitronaphthylamines.

A. J. BOULTON and A. R. KATRITZKY: The tautomerism of heteroaromatic compounds with five-membered rings—I. 5-Hydroxy-isoxazoles–isoxazol-5-ones.

A. J. BOULTON and A. R. KATRITZKY: The tautomerism of heteroaromatic compounds with five-membered rings—II. 3-, 4- and 5-Amino- and -acetamido-isoxazoles.

D. N. KIRK and V. PETROV: The stereochemistry of some halogenecholestan-3-ones.

B. MAJHOFER-OREŠČANIN and M. PROSTENIK: Studies in the sphingolipids series—XVII. Synthesis and resolution of erythro and threo-C_{20}-dihydrosphingosines.

L. PICHAT, M. HERBERT et M. THIERS: Etudes sur les méthodes de préparation de la selenocystamine, selenohypotaurine et selenotaurine.

T. R. GOVINDACHARI, B. R. PAI, K. K. PURUSHOTHAMAN and S. RAJADURAI: Structure and stereochemistry of jatamansone.

N. PETRAGNANI: Aryl tellurium trihalides—II. Condensation reaction with methyl ketones and aromatic compounds containing electron-repelling groups.

KATSUMI KOTERA: The stereochemistry of lycorane-III (—)β-lycorane.

KATSUMI KOTERA: The stereochemistry of lycorane-III γ- and δ-lycorane.

G. KRESZE und G. SCHULZ: Additionsreaktionen der Nitrosogruppe—II. Diels–Alder-Reaktion mit Cyclischen; Synthese einiger *Cis*-4-phenylaminocyclanole.

P. YATES and P. EATON: The rearrangement of 4,5,6,7-tetrachloro-3a,4,7,7a-tetrahydro-4,7-methanoinden-8-one.

Z. KECKI: The role of acidity in the kinetics of aromatic compound nitration.

J. W. POWELL and M. C. WHITING: The decomposition of sulphon–hydrazone salts: mechanism and stereochemistry—II. The pyrolysis of the diazodecalins.

J. W. POWELL and M. C. WHITING: The analysis of mixtures of octalines.

H. C. BROWN: Hydroboration—a powerful synthetic tool.

K. AGHORAMURTHY, K. G. SARMA and T. R. SESHADRI: Chemical investigations of Indian lichens —XXIV. The chemical components of *Alectoria virens Tayl.* Constitution of a new depsidone, virensic acid.